Sheet no. : 13

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Herpes viruses :

They are a large group of viruses , widely distributed in the nature .

To some extend herpes viruses , respiratory viruses , and HPV are the most spread in the community , and easy to be acquired especially certain types of herpes viruses which is considered the most common , there is no single person who has not acquired infection with at least herpes type simplex one .

Basic structure :

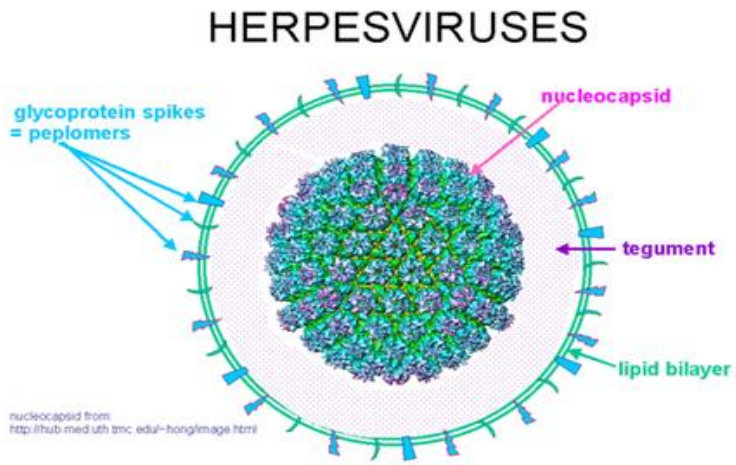
As you can see in the picture, we have in the center the presence of genome , the genome is composed of Ds-DNA , not as single stranded viruses , it may be segmented with in the genome . associated with the genome the presence of capsid , the capsid is composed of large number of copsomeres up to 162 capsomeres , these capsomeres are surrounded by special layer of specific protein called tegument .

Tegument : a special protein which surround the genome

and responsible for the mechanism of attachment (in

addition to the spikes) , the mechanism of replication,

mechanism of releasing from cell



membrane of nucleus cell

as well as the outer membrane of the cell

** Ds-DNA viruses replicate within the nucleus , but in order

to produce the necessary protein structure , the process is

slow , it's not easy , and not like other viruses , it takes many steps to be completed , then later to be released first from nucleus of the infected cells , then from the outer membrane of the infected cells . At the end , the infection results in the lysis of the cell (lysis of the cell mean killing effect) , there for herpes viruses normally associated with replication in the infected cells , and at the same time with severe damage of the infected cells .

Not all herpes viruses result in complete replication in the nucleus of the infected cells , which means we might be infected with herpes cells without developing the features of herpes lesion at the end , that can be recognized in epithelial cells and mucosal cells , this mean the non infectious processes or non infectious end results is more common than the infectious results that result in the release of new viral particles , which mean that the potential of herpes viruses to produce infectious particles in the infected tissues almost less than 50 % , so contact with herpes viruses is not necessary to be associated with developing of clinical features of herpes infection .

- During the replication with in the nucleus , teguments and DNA sequence are responsible for the production of 18 – 100 specific types of protein , which are important to produce a new viral particles , and this is very much in comparison with other viruses like influenza viruses , rhinoviruses , and others . usually only 15 or 20 specific protein is enough to produce new virus particles . This means that herpes viruses have more complex mechanism of replication , and you will see later that it might be associated with latency in the infected tissue .

latency : is very important aspect of herpes infection , and it means that the infected nucleus of the epithelial cells in general may have one of two possibility end result :

release of the virus and developing of clinical features of the infection .

without your recognition , some part of the genome of the herpes viruses become integrated with the genome of the infected cells . it might be associated with extrachromosomal episome .

In Bactria we have plasmid that can be associated with antibiotic resistant , and with the production of entrotoxins ,and other function , and we have episomes , but in relation to bacteria we don't usually use the term episome , instead we use another terms like integrome , which means small segment of DNA which manage to be integrated in

the bacterial chromosome . in viruses we don't use the term integrome , we use the term of episomes . episome is not like plasmid , not self replicating of genetic material (can't replicate alone) , it must be attached to the cell chromosome as extracellular attachment , or may be integrated , if it is integrated with in choromosome of the infected cell this mean we have stable recombination , and it won't be easy later to separate it , it will be always replicated _under certain condition_ with the replication of the infected cell chromosome , this mean at any time there will be repeat reoccurrence of the infection with herpes , any time you may recognize the eruption of herpes infection , in the form of lesions , in form of type of the disease .

where as the presence of episomes , mostly will be separated . the patient will recover , and he won't experience the reoccurrence of infection , this is the difference between them , but they both are associated with latency , and latency of the virus is so important . without the presence of this latency herpes viruses don't cause serious type of diseases .

<u>Herpes groups :</u>

we have eight groups

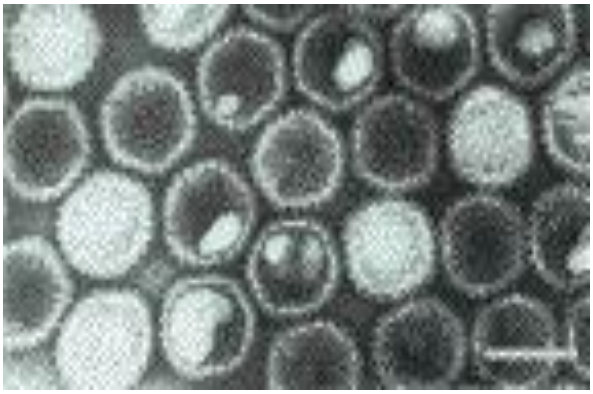
1. Alpha-herpesviruses : represented by HSV-1 (herpes simplex one) and HSV-2 .

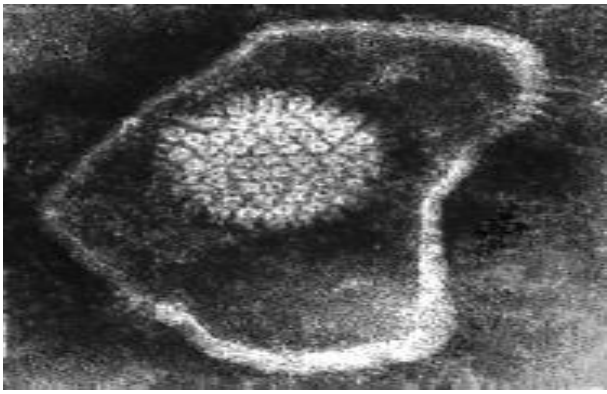
The difference between first and the second is the sequence of DNA of the herpes viruses . these two have 70% of their DNA sequence is homology , which mean that they have very common features , common mechanism of disease , and so on .

** HSV1 and HSV2 are associated with human infection only , they might be transmitted to animals and found in the animals , but without the presence of specific types of disease .

- in relation to multiplication, or the incubation period of these viruses (HSV1 and 2) , they slowly replicate with in the infected tissue . time of replication between 8 – 16 hour . in comparison to other viruses like influenza , influenza have shorter incubation period , which is related to the replication of the viruses that later affect the incubation period of the disease . incubation period differ than replication period with in the nucleus . 8 – 16 hours mean developing of herpes disease may be recognized after one to three weeks generally , and this differ because we have different types of viruses . replication can be easily recognized with in the infected tissue by the presence of nuclear inclusion bodies (first to be recognized) , later we recognize the presence of Multinucleate giant cells .

* In the pictures below you can see once there is infection in the epithelial cells or in skin or mucosa , we have elongated multinucleated cells . also, you can see large ballooning cells , and all these are recognized during the process of infection in the mucosa or in epithelial skin infection and so on .





- Generally the multiplication for the viruses , result in lysis of the cell _ which mean death of the cell _ and this allow the viruses easily to spread and produce with in short period more and more damage to the epithelial cells or mucosal cells , (depend on the type of the infected cells) .

- Some times it is not easy to distinguish clinically between infection by type one and type two , despite the fact the type 1 is more related to the oral cavity , and type 2 is more related to genital tract . but the oral cavity might be under certain conditions

infected with type 2 , also genital tract can be infected with type 1 , so the only way to be sure 100% about the causative herpes type , you have to do molecular technique , to prove whether it's type 1 or type 2 . however in the past they used to recognize and report if it's in the oral cavity it is type 1 , but recently they found 2- 5 % of the oral herpes manifestation might be due to type 2 , which mean there is a change or developing in the infection of herpes simplex . so anyone of us who will see any lesion on the lips or on oral mucosa , will think that this is type 1 herpes , but this is not always true because it might be type 2 , with the same clinical features . Again type 1 is associated with 90 % or more of the lesion in the oral cavity , mucosa of oral cavity , and it might spread to the mucosa of the nose , mucosa of the eye , and rarely the viruses may reach blood stream , and CNS ((this in relation to type 1)) . type 2 is more associated with viraemia _ blood sepsis _ , more associated with CNS infection , not from the oral cavity , it can be from genital tract or respiratory tract .

- Most common lesion which is recognized in herpes 2 is vesicle eruption , vesicle eruption means : ballooning of the epithelial cells , and this associated with ballooning or inclusion bodies , etc , and slowly produce later more inflammatory reaction , which can be recognized as lesions or ulcers . the presence of ulcers can persist for few days , and disappear after few days , or it may be associated with fever and lymphadenopathy . specially in children , often the presence of vesicle eruption in the oral cavity will be associated with lymphadenopathy and fever , which give the impression that the child may have sore throat , although he doesn't have any inflammation of the tonsils .. etc , his infection is related only to the mucosa of the oral cavity , and this may persist for 1 -2 weeks, most often 8 – 12 days , after that the lesion slowly become less intense and disappear without presence of any damage in the infected mucosa that can be recognized . in general all children up to age of 5 years may be easily infected with herpes type 1 , but not after 6 months of birth , because they are immune , due to the presence of maternal anti herpes bodies , which protect them against acquiring infection and developing of vesicle eruption and oral mucosa infection with herpes viruses , but after 6 months they become susceptible , and often with in 5 years , the majority of children will acquire infection with herpes simplex 1 at least .

Herpes 1 and 2:
features of latency is similar but it depends on the type of ganglia, it's either orofacial ganglia (upper part of the body) or genital ganglia (lower part of the body).

We've mentioned that primary mucous infection is 99% related to herpes (1), in any part of the oral mucosa if there are ulcerative vesicles or lesions, which mean eruption of the epithelial cells, filled with fluids and few pus cells, this lesion persists generally in children for one week and disappears. In majority of cases, disappearing doesn't mean that the virus is totally eliminated or eradicated from the body. Rarely, there's 100% elimination, this 100% elimination needs intensive immune response that can't be developed within one week, it may need 2-3 months to produce sufficient and specific antibody (IgA)?? *later the doctor mentions IgG, not IgA ,,,* in order to control multiplication of the virus and prevent the remaining of the virus in the body, {this is difficult to achieve in infants and children}.

Primary herpes lesion develops in oral cavity and later, spreads from the site of infection to the trigeminal ganglia where the virus will be mainly integrated in form of episomes –small segments of DNA will be attached to the chromosomal DNA of the nerve cells-, rarely, these small segments of the virus would be integrated and became a recombinant within the chromosomal DNA. This means that at least 1% of the nerve cells of the trigeminal ganglion will carry the genes of herpes to reproduce it.

Following stimulation factors are either inside or outside factors, examples of outside factors are sun light, U.V, certain drugs,,,, whereas internal factors are hormones (menstrual lady), stress conditions, immunodeficiency,,,,. These factors contribute to reactivation of the herpes inside the trigeminal ganglion, allowing the viral particles to be released and travelled along the axon to the primary site of infection, inside the oral cavity, resulting in repeating developing of the vesicles, lesions and ulcerations. This is known as Recurrent HSV-1 infection.

Latent form and reactivation will not develop in all infected patients with herpes, only (5-10) % of them. How many times this recurrence would occur depends on the immune response of the infected patient, if he has managed to produce specific types of Igg and delayed type of hypersensitivity.

The recurrence will be limited to one or two times in a year or in 2-3 years, according to the availability of the internal and external stimuli.

One important feature in relation to virus reactivation in specific type of patients, if these patients suffer from immunocompromised conditions, they might develop complications.

Generally, reactivation is not necessary to be associated with eruption of vesicles inside the oral cavity, the patient might be asymptomatic, he may have fever, erythema on the lips and inside the oral mucosa, and often this this means that the virus is already excreted from the oral cavity and this patient might be a source of infection. Recurrent infection could be symptomatic; in immunodeficiency patient symptomatic recurrence might be associated with dissemination of the virus to the blood and internal organs causing aseptic meningitis and Encephalitis and can be fatal.

Common herpes Disease usually recognized in children and it's less in adults:

Mucocutaneous lesions, at the lips, oral cavity, skin under the hair, nose and might spread to the eyes. This is related to 99% to HSV-1
^^in recent study, they find that more and more cutaneous lesions have been related to HSV-2 around (5-10)% , this means that genital herpes (type2) has been contributed with HSV-1 to the mucocutaneous lesions^^ at the exam it's 99% related to HSV -1 this recent study is just to nourish your amazing knowledge :3

Gengivostomatitis, HSV can affect any part of the mucosa, soft palate, gingiva, tongue, oropharynx ~more sever~, mostly recognized in children less than 5 years.
Herpetic stomatitis, often older children with more sever ulceration, so it might disseminate to the blood and reach the internal organs.

Primary lesion is often recognized at the junction of the lips or spread to the nose and if you look inside the oral cavity you may not recognize any lesion.

In children it might reach conjunctiva and produce Herpes Conjunctivitis and might cause severe infection at the cornea, which is very dangerous.

**Herpes Keratitis is very rare 0.1% in relation to the eye caused mainly by HSV-1, it developed following conjunctivitis. ^~HSV-2 can cause it and it's much more severe~^

Herpes Keratitis associated with keratoconjunctivitis and corneal ulceration and this should treated within short period as early as possible, otherwise, it might cause corneal damage and affect the vision leading to blindness.

**skin manifestations, it needs professional expert to recognize it, 90% of cases affect the dentist :3 and surgeons, because in asymptomatic herpes infection, there's no lesion inside the oral cavity but you have viral particle in saliva, so you must not use your finger, you should wear gloves, because you might have small injuries at your skin and you might be infected and have very painful ulceration at your index or thumb known as herpetic whitlow and it's very difficult to treat and may persist for one month and may be associated with fever and adenopathy and so forth.

**Eczema herpeticum, is found in babies, we have 2 types of bacteria that cause impetigo; staph.aures and strep.type A, impetigo is a damage of the layers of the skin and if this damage is contaminated with herpes, might produce Eczema herpeticum and it's no easily to treat, the patient (infant) might suffer from complications; gastrointestinal symptoms, fever, may reach the blood and produce meningitis and Encephalitis.

Eczema herpeticum is a fatal disease>.< especially in infants or immunocompromized and might cause hemorrhagic necrosis inside the brain.

Immunoresponse to HSV infection:

‘’’primary infection in children, resulted in developing of specific immunity mainly IGg against glycoprotein of the virus.

‘’’during infection, the body (before production of antibody that requires a week) responds by production of natural killing, cytotoxic cells, T helper lymphocyte which is responsible of delayed type hypersensitivity.

$~specific Antibody, level different from one to another.

$~Delayed hypersensitivity.

There's something unique to HSV-2:

HSV-1 and HSV-2 are similar in 70% of their structure; due to this homology HSV-2 manage to prevent infection with HSV-1. The specific antibody is enough to prevent recurrence infection of HSV-1, where HSV-1 can't do this job, why??? Nobody knows :3

Genital Herpes:

HSV-1, oral cavity but might affect the genital tract but much more less, around (5%) but the majority related to HSV-2.

In primary infection in females and males, it can be associated with extra and intra genital.

<<in males, it's more associated with extra genital tract and might spread to the rectum and affect other part of the body; oral cavity, the infection is easily to be recognized because it's extra genital, males may suffer from urethritis, burning sensation during urination and may be no symptoms at all and discovered during examination.

<< in females, it's more associated with internal genital tract, cervix more than vagina and labia, infection is difficult to be recognized, asymptomatic is very high more than 50%, and often discovered by chance or during delivery, that might lead to neonatal herpes.

You can take swap and look for herpes DNA, it's the simplest and best method and very specific because in relation to serological test, you might not discover the Antibody and you may be confused if it's infection or not, because the general population have specific Antibody titer is often normal and if this titer is elevated you require 2 to 3 tests to recognize the infection with the herpes so it's not that good.

Recurrence of the genital herpes is 3-6 times more common in females, treatment might not be successful, only it reduces the severity of the infection and ulceration.

If a pregnant lady is infected with herpes wither it's recognized or not, this might result in neonate herpes.

Neonatal herpes means that the virus might reach the respiratory tract producing pneumonitis, might reach the eyes producing conjunctivitis and from the eye may swim to the blood producing meningitis and Encephalitis.

During delivery, if the physician recognizes the presence of ulceration, he has to treat the infant immediately with prophylactic anti-viral drugs and more better to get the delivery by the cesarean section. Keep in mind that direct neonatal herpes from the mother is associated with less than 1% of cases, the more common is infection later to delivery, through the contact with other infected people; doctor, nurses,,,,.

In addition don't let your baby being a carrier and spreads the infection to others, because it's much more hard and difficult to treat.

~~3 common complications in acquired neonatal herpes (NOT from the mother):

Conjunctivitis, oral and skin infection
May disseminate to the blood producing meningitis and Encephalitis
General sepsis, pneumonia <easily recognized, the baby would have poor feeding>, more dangerous if he develops jaundice, meaning that the virus reaches the liver, skin lesion may occur, all these have high mortality.

^.^Diagnosis and treatment of HSV-1,2:

''Again _-_ the best method is to use direct DNA detection from the serum.

''Culture is not used as routine technique; it's mainly for research and to detect the developing of resistance.

10% of isolated strains of herpes from many countries prove to be resistance to common types of anti-viral drugs (Aciclovir, Valaciclovir).

Treatment of keratoconjunctivitis at optichen is very important.

Few drugs are available for treatment of herpes infection.

''Serology, if you have enough specific antibody against herpes infection, it's difficult because all of us has certain amount of antibody, so in order to recognize if there's elevation or not, you must at least measure 2-3 times your herpes antibody from the blood sample, these antibody might not be elevated in some people indicating such people are suspitable to develop herpes infection.

<>There's NO vaccine<>.

~.~Treatment:

-Topical, at the first lesion

-Anti-viral drugs (Aciclovir), they must be given at the first 24-48 hours following presence of first developing of vesicle, without delay

-I.V treatment at the hospital.