**Herpes viruses lecture -6-**

 **HerpesViruses**

* The herpes virus family contains several of the most important human pathogens. clinically the virus exhibit human pathogens with spectrum of diseases. Some have a wide host range, where are others have a narrow host range
* The outstanding property of herpes viruses is their ability to establish lifelong persistent infections in their hosts and to undergo periodic reactivation.
* Herpes viruses that are commonly infect humans include:-
1. Herpes simplex viruses type 1&2.
2. Varicella- Zoster virus.
3. Cytomegalovirus(CMV).
4. Human herpes viruses 6,7
5. Epstein- Barr viruses.
6. Kaposis sarcoma associated herpes virus.
7. Herpes B virus of monkey can also infect human.

**Properties of Herpes viruses :-**

1. Virion: Spherical,
2. Genome: dsDNA, Linear.
3. Protein: more than 35proteins in virion .
4. Envelope:- contain viral glycoprotein and Fc receptor .
5. Replication:- in the nucleus and bud from the nuclear membrane.

**Classification:**

Classified into three sub families – based on physical & genitical properties:- 1. **Alpha Herpes :** They have rapid replicate cycle (12-18 hrs). It is variable host range. These viruses tendency to form latency in sensory ganglia. Produced rapid CPE & release virus from the infected cells Ex: HSV-1, HSV-2 , VZV (**Varicella-Zoster Virus**).

2. **Beta Herpes :** They have narrow host range. Has slow replication cycle (more than 24 hrs). **Ex: Cytomegalovirus**Virus (CMV),

HHV-6, HHV-7

3. **Gama Herpes :** They infected lymphoid tissue & causes latency in lymphocyte. Ex : Epstein-Barr Virus (EBV), HHV-8

**Morphology**

All Herpes viruses virions have four structural :- **Core, Capsid** , **Tegument** , **Envelope** .



**Figure (1): show the morphology of HSV**

**Herpes viruses infection in human**

**1) Herpes simplex viruses (HSV)**

* **Properties of the viruses**

a) HSV is a wide spread in human, it has a wide host range and can infect many different animals in addition to human.

b) It has two types 1&2 , there genome are similar in organization and share 50 - 70% homology , but they can distinguishesd by restriction enzyme analysis of viral DNA.

c) It is able to replicate in many types of cells and they grow rapidly , also it is highly cytolytic .

d) Double stranded DNA enveloped virus with a genome of around 150 kp.

**Mode of Transmition**

**HSV-1** transmited by direct contact with infected saliva , skin lesions or respiratory secretions.

**HSV-2** is transmited sexually (Venereal disease) and also from maternal genital to newborn (Perinatal**).**

* **Pathology**

The virus is cytolytic and lead for the formation of ballooning of infected cells and the formation of intracellular inclusion bodies.

* **Pathogenesis**

**a) primary infection**

Herpes simplex is one of the most common viral infections in humans. Primary infection is usually acquired in early childhood , between two and five years of age. Humans are the only natural hosts. Asymptomatic carriers form the more important source of infection.

The virus enters through defects or broken in the skin or mucous membranes and multiplies locally with cell-to cell spread. The virus enters cutaneous nerve fibres and is transported intra-axonally to the dorsal root ganglia where it replicates. migration of the virus can take place from the ganglia to the skin and mucosa to cause cutaneous and mucosal lesions. The virus remains latent in the ganglia to be reactivated periodically in some individuals causing recurrent oral and genital lesions. **HSV-1** it is limited to the oropharynx but **HSV-2** occured in the genital tract.

**b) latent infection**

HSV have ability to stay as latent virus in infected cells for life time. The stimuli or trigger which is lead for the reactivation of the latent virus are :-

1. Axonal injury
2. Fever
3. Physical or emotion al stress.
4. Exposure to ultraviolet , sunlight
5. infection especially pneumococcal and meningococcal.
* **Laboratory diagnosis :-**

**1- Direct Detection**

- Take a scraping from the base of the vesicles and stain it with Giemsa stain and examine under light microscope or Electron microscope to see the multinucleated giant.

- Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV, Immunofluorescence of skin scrapping - can distinguish between HSV and VZV.

**2- PCR** - Now used routinely for the diagnosis of herpes simplex encephalitis

**3- Virus Isolation**

HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days

**3- Serology** use to detect (IgM&IgG) after 4-7 days by ELISA test.

**2- Varicella-Zoster Virus (VZV)/ Human Herpes virus 3**

**Transmission**:- Direct contact, Respiratory droplet.

**Diseases** :- Two disease caused by **Varicella-Zoster Virus:-**

**1-Varicella( Chicken Pox)** :- It is the acute disease that occurred by the primary contact with the virus which include Erythematous ulcerating encrusting vesicles beginning on the face and trunk and then progressing towards the extremities, as well as mucous membranes and

Presents fever, lymphadenopathy. Spontaneously resolves in < 1 week.

2- **Zoster** **( shingles)** it is disease occur in response to the reactivation of latent VZV in neurons in sensory ganglia.

**Pathogenesis and clinical features:-**

**a)Varicella**

The infection is occur through the mucosa of the conjunctiva and upper respiratory tract followed by initial replication in the regional lymph node then after primary and secondary viremia the virus transported by the mononuclear cells to the skin this associated with typical vesicles of chicken pox.

**b) Zoster**

The lesions of Zoster are histopathologically identical to those of varicella . the lesion is closely to the areas of innervation of dorsal root ganglia . the reactivation is occurred as a result of lowering of immunity which allows for replication of the virus and then it travel down with the nerve to the skin and induce vesicle formation .

**Laboratory diagnosis :-**

**1-Direct detection**

staining of the smear which has been taken from the base of the vesicle and examine under the microscope to see a multinucleate giant cell**.**

**2- Virus Isolation:-**

culture of the vesicle fluid in human cell .

**3- serology**

**Elisa or IF test by detect antibodies.** the presence of VZV IgG is indicative of past infection and immunity. The presence of IgM is indicative of recent primary infection.

**3-Epstein-Barr Virus (EBV) /Human Herpes virus 4**

**Properties of the virus :-** there are two types of EBV (EBV1&2) based on the differences in the latency nuclear antigen genes (EBNAs, EBERs).

**A)Biology of EBV :-**

The major target cell for EBV is the B lymphocytes. The infection occur by binding of the virus with the CD21 receptor of the B lymphocyte. Then the virus will enter directly a latent state in the lymphocyte without undergoing a period of complete viral replication .

EBV –immortalized B lymphocytes express differentiated functions such as :-

1- Secretion of I.g ( Immunoglobulin)

2- B cell activation products (e.g CD23) are also expressed.

3- Ten viral gene products are expressed including six different EBV nuclear antigens (EBNA-1, 2, -3A, 3B , 3C, and leader protein (EBNA-LP), two later membrane proteins (LMP-1,LMP-2) and two small untranslated RNAs (EBER 1& 2) →EBV encoded RNA . at any given time the latency will stop and the virus start to replicate in the cell by a variety of stimuli .

**B) Viral Antigen :-**

EBV antigens are divided into 3 classes :-

1) **Latent phase antigens :**- EBNAs & LMPs.

2) **Early antigens :-** are non structural proteins who synthesis is not dependent on viral DNA replication . the expression of these antigens indicates the onset od productive viral replication.

**3) Late antigens :-** are the structural component of the viral capsid**.**

**and pathology:- Pathogensis**

**A) Primary infection**

EBV is transmitted by infected saliva (the kissing disease) .Infection starts in the oropharynx by replication the virus in epithelial cell then spreads to the blood. In blood , the virus infects B lymphocytes. • In B lymphocytes, viral DNA integrates in cell genome. After primary infection, EBV maintains a steady low grade latent infection in the body. Primary infection in children are usually subclinical but if they occur in young adults develop Infectious Mononucleosis (I.M) the typical antibody produce with disease is the heterophil antibody that react with antigen on sheep RBC **( Monospot test)** .

B) Reactivation from Latency.

C) Tumors

EBV is the tumor virus number one as has been reported by the WHO.

**Clinical findings:-**

**1-** Infectious Mononucleosis

 self-limited disease which consists of Fever, headache, severe pharyngitis, splenomegaly and generalized Lymphadenomegaly.

**2-** Oral hairyleukoplakia

**3-** Nasopharyngeal Carcinoma.

4- Burkitt Lymphoma.

5-Lymphoproliferative disease and lymphoma in the immunodeficiency host.

6- Gastric carcinoma

7- prostate carcinoma

8- Breast carcinoma

9- Hodgkin lymphoma

**Laboratory diagnosis :-**

A) Isolation and identification

1-Nucleic acid hybridization is the most sensitive methods for detecting EBV by targeting EBERs .

2-EBV can be isolated from saliva, peripheral blood by immortalization of normal human lymphocytes, this assay is time consuming (6-8) weeks.

3- PCR

B) Serology :- by ELISA , IIFT

1) In acute disease :- a transient rise in IgM to VCA (viral capsid antigen)

2- within weeks replaced by IgG to VCA which persist for life .

3) Slightly later AB to several EA (early antigen) develop that persist for several months.

4- Several weeks after acute infection AB to EBNA and membrane Ag rise and persist throughout life .

**Prevention & treatment :-**

No vaccine to EBV available . Acyclovir reduce EBV shedding but has no effect on symptoms.

**4- Cytomegalovirus (CMV)** / **Human Herpes virus 5**

CMV are ubiquitous herpes viruses that are common causes of human disease. The name for classic cytomegalic inclusion disease, derive from the massive enlargement of CMV infected cells.

**Properties of the virus :-**

1- It has the largest genetic content of the human herpesviruses.

2- CMV are very species specific and cell type specific.

3- Human CMV replicates in vitro only in human fibroblast.

4- CMV produces characteristic cytopathic effect perinuclear cytoplasmic inclusion form in addition to the intranuclear inclusion typical of herpes viruses.

5- It is the only virus have ability to infect the kidney.

**Pathogenesis , Pathology , clinical findings**

**1) Normal host**

CMV may be transmitted from infected person to person by close contact with virus bearing material **(**saliva , blood , urine, semen, cervical/vaginal secretions or breast milk and Perinatal. After 4-8 weeks the virus produce systemic infection . primary CMV infection of older children and adults usually asymptomatic but occasionally causes spontaneous I.M syndrome.

**B) Immunocompromised host**

The primary infection is more severe than in normal . pneumonia is the most common complication . virus associated leukopenia is common in solid organ transplant recipients also CMV related rejection of renal transplants .

**C) Congenital and Perinatal infection**

Fetal and newborn infections with CMV may be sever. A high percentage of babies with this disease will exhibit developmental defects and mental retardation . the virus can be transmitted in utro with both primary and reactivated maternal infection.generalized cytomegalic inclusion disease results most often from primary maternal infection . fetal damage seldom results from reactivated maternal infections. The infection of the infant remain subclinical though chronic.

Mortality rates can reach up to 30% , Majority of the survivor with develop significant CNS defects within 2years. About 10% will develop deafness.

**NOTE :-** the virus usually shed in saliva and urine for weeks or months after infection.

**Laboratory Diagnosis :-**

**A - PCR and antigen detection**

PCR assay have replaced virus isolation and culture (too slow) . the PCR assays are design to detect replicating virus , not latent viral genomes. blood and urine are most commonly tested .

**B- Isolation of the virus**

Human fibroblast are used for virus isolation .

**C- Serology** :- detection of IgG indicated past infection potential for undergo reactivation .detection of IgM AB suggest current infection.

**Treatment**

 Ganciclovir used specifically in immunocomprimised patients.

Acyclovir and valacyclovir have shown some benefits in bone marrow and renal transplantation .