SHEET NO. 6

MICROBIOLOGY (Virology)

DOCTOR 2019 | MEDICINE | JU

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In today's lecture we will talk about the second part of viruses in the family "Herpesviridae" We will explain those viruses:

- EBV (Epstein-Barr virus, HHV4)
- CMV (Cytomegalo Virus, HHV5)
- Human Herpes Viruses 6 & 7 (HHV6, HHV7)
- Kaposi Sarcoma-associated herpes virus (HHV8)

Epstein-Barr Virus (EBV)

General Information

- It was discovered by Michael Anthony Epstein with his student Yvonne Barr, they knew that the virus is associated with Burkitt Lymphoma and it was the first Oncovirus discovered in human population.
  Burkitt Lymphoma: cancer in B lymphocytes; due to excessive division of the EBV-infected cells.
  Oncovirus: An oncovirus is a virus that can cause cancer.
- Linear, double stranded DNA virus.
- Genome size: 172 Kb pair.
- Subfamily: Gamma herpes virinae.
- Genus: *Lymphocryptoviral*
- EBV is the closest to HHV8; both are classified under the subfamily "Gamma herpes virinae".

Epidemiology

- Developing Countries ➔ EBV occurs in the first decade of an individual, due to crowded places and low hygienic procedures.
- Developed Countries ➔ EBV occurs late after puberty.
  50% of a developed country population reach puberty and they haven't acquired EBV yet, and the infection percentage starts increasing by reaching puberty, by sexual transmission or kissing.

Transmission:

1. Saliva; and that is why it is called "Kissing Disease",
2. direct contact with a person shedding the virus (able to transmit it),
3. sexual contact.

Tropism

- **EBV Mainly infects B lymphocytes**, since they are the only cells that have the main receptor of EBV.
  ➔ The receptor of EBV is **CD21** or called complement receptor 2 (**CR2**).
- Epithelial cells can be infected with EBV.
- Monocytes have a low probability to also get infected.
- **When EBV infect an individual, it transforms the mature B lymphocyte to Lymphoblastoid cell lines that are capable of indefinite growth, with a predominance of large, atypical T lymphocytes (they are cytotoxic T cells that have responded and recognized infected B cells that have expressed MHC1).**

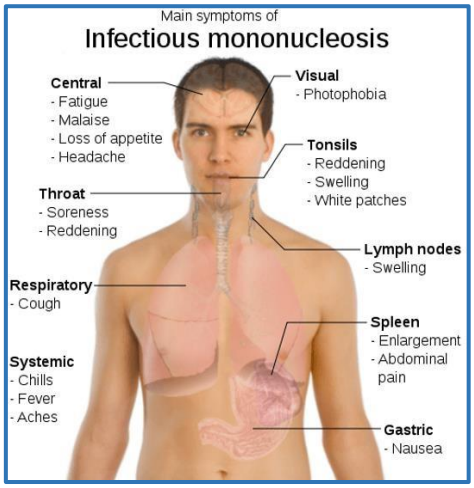
Latency: the ability of a virus to lie dormant within the cell, and get activated later.

- in general, Latency is a very important and common feature of all herpes viridae viruses.
  HSV-1, HSV-2, VZV ➔ when they under go latent infection, they infect a different place of the body, from the place of the primary infection.
  EBV ➔ when it undergo latent infection, it affect the same place of the body, which is: B cells.
  Thus, B cells are the only site of latency in EBV.

Clinical Features and Symptoms

- Incubation Phase is about 1-4 weeks, and could extend more, reaching 50 days. After this, symptoms start to show up, Low-grade fever and malaise may persist for weeks to months after acute illness.
- Although Complications or fatality is rare in NORMAL hosts, fatality may occur due to a rupture or trauma to the Massive spleen, causing hemorrhage.
- EBV causes Infectious Mononucleosis (IMN)
  other viruses like: HSV-1 or CMV, and non-viral agents can also cause IMN.
- Infectious mononucleosis symptoms: pharyngitis with fever, malaise, lymphadenopathy, fatigue, systemic symptoms, head and body aches, sore throat.
- EBV is also associated with various non-malignant, premalignant, and malignant diseases. Malignant diseases: lymphoproliferative diseases (over and uncontrolled production of lymphocytes) such as Burkitt lymphoma (malignant).
- EBV in immunocompromised patients or HIV patients, is very severe and can easily cause fatality, since the immune system is completely absent.
- EBV-negative patients who are receiving transplantation grafts from EBV-positive patients, are at high risk of developing a number of lymphoproliferative disorders after transplantation.

- sometimes EBV show skin eruptions as a symptom.
- This manifestation is specific in infected **HIV patients** or **Immunocompromised patients**: **oral hairy leukoplakia (white patches on the side of the tongue with a corrugated or hairy appearance, it is benign)**



1. **non-malignant conditions:**
   - Children (first decade of life): the majority undergo asymptomatic infection.
   - adults:
   50 % manifest symptoms, the classical manifestation of primary infection is infectious mononucleosis and its symptoms which are mainly immune mediated. symptoms are in the figure ➔
   50% do not manifest symptoms.
2. **Malignant conditions:**

- **lymphoproliferative diseases and lymphomas of different types** like**:**
  - Burkitt lymphoma (>95% of BL patients have past-infection of EBV)
  - Hodgkin's lymphoma (>50% of HL have past-infection of EBV)
- **non-lymphoid malignancies** such as**:**
  - Gastric carcinoma (>10% of GC have past-infection of EBV)
  - Nasopharyngeal carcinoma (> 90% of NPC patients have past-infection of EBV)

very high relation between the infection of EBV and certain types of tumors

Diagnosis

Tests that detect EBV are:

1. **Nucleic acid detection by PCR**
2. **Serology**
3. **Heterophile antibody test**
   - *Heterophile antibodies are antibodies induced by external antigens.*
   - Very common way, because 85% of EBV-infected individuals have heterophile antibodies, which makes the test able to succeed.
   - **Process**: it **measures** the existence of **antibodies** produced after EBV infection, by **detecting** if those antibodies can **react** with **R**ed **B**lood **C**ells **antigens**. Those RBCs are brought from different species such as: sheep/horse/cow.
   - sometimes, HAT test false positive (test wrongly that a person is infected) Justification: the test may have detected a CMV antibody instead of EBV.
4. **VCA (Viral Capsid Antigen),** they are two types:
   - **VCA IgG** ➔ marker of **PREVIOUS** exposure to EBV**,** appears in the acute phase of EBV infection, declines slightly then persists for the rest of a person's life.
   - **VCA IgM** ➔ marker of a primary acute **ONGOING** infection, appears early in EBV infection and usually disappears after onset of symptoms.

5. **EBNA (Epstein-Barr Nuclear Antigen)**
   If this test arises positive, and all of the rest tests were negative, then this is an indication of primary acute **ONGOING** infection, appears after onset of symptoms and persists for the rest of a person's life.

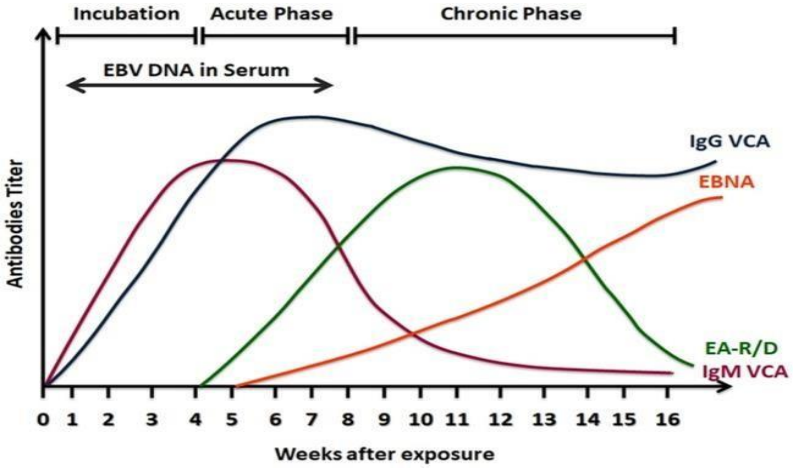
> We divide EBV into two types, **depending on its Nuclear antigens**, Type A (more prevalent and associated with infectious mononucleosis with most infected people) and Type B. And since there are two types, we can predict that an individual could be infected with type A then type B, which is common especially in Immunocompromised individuals.

6. **EA-R /EA-D (Early Antigens either Restricted or Diffused)**
   An indication of primary acute **ONGOING** infection OR of a **RECENT** infection, but after several weeks, they will disappear.

So, for Acute Primary ONGOING infection, we use VCA IgM and EBNA and EA-R/D

7. **Blood test which shows:**
   -thrombocytopenia (low platelets level)
   -granulocytopenia
   -anemia

Click here to watch a very good video that summarizes EBV Testing ☺

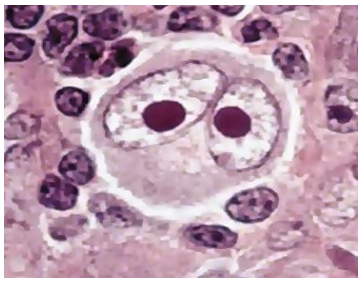


Treatment

- there is no EBV vaccine but trials are taking place by neutralizing antibodies.
- although drugs are not that much needed in Infectious Mononucleosis, but some are used to **reduce EBV replication** and those drugs are grouped into three:
  1- nucleoside analog such as ganciclovir, valganciclovir, acyclovir, valaciclovir,
  2- acyclic nucleotide analog such as cidofovir and adefovir, غير داخل
  3- pyrophosphate analog such as foscarnet.

Cytomegalo Virus (CMV)

General Information



- most common cause of congenital infection.
- Subfamily: Beta herpes virinae. Like HHV6 & HHV7.

Epidemiology

- CMV sero-prevalence varies with socioeconomic status, living conditions, and hygienic practices by 50%-100%, so most of people have been exposed to CMV infection.

Transmission:

- Vertically: mother to child, transmission can be either before or during or after birth, since its shedding period occurs in different places in the body, including breast milk. And this causes asymptomatic infection to the infant, but it may **later** develop neurological degeneration symptoms, developmental delays, mental retardation or neurosensory deafness (hearing-loss).
  -10% are symptomatic in birth.
- Horizontally: through direct contact by the fecal–oral route and usually by ingestion of contaminated water or foods.
- important place of shedding is blood, so if a previously-infected person is experiencing reactivation (where no symptoms manifest \ يعني هو بعرفش انه بيعدي) and donated blood, for an immunocompromised patient/ had an organ transplantation, then it will undergo a very severe Infectious mononucleosis.

Tropism

- target cells are the epithelial cells,. cellular glands, different types of red blood cells and fibroblasts.

Latency

- Latency site of CMV is progenitors in Bone marrow specifically in myeloid stem cells.

Clinical Features & symptoms

- The infection is very common but mostly asymptomatic.
- The infection develops a mononucleosis-like illness symptom.
- The infection is more sever in immunocompromised individuals and neonates.

- **In immunocompromised patients** and HIV patients (virus hijacks T-cells, so we have decrease in their number). The decrease in **T-CD4+ (helper)** –conc.50µ/ml– leads to increasing the severity of CMV infection,this produces many manifestations like:
  a. Retinitis (inflammation of the retina) as shown in the picture
  b. pancreatitis
  c. Hepatitis
  d. GI diseases – esophagitis
  e. Encephalitis (brain inflammation)

- **In Neonates**, 0.2%-2.5% of infants of all births get infected with CMV, which makes it the most common cause of congenital infections (from the TORCH agents). The infection can be fatal.

  10% of those infants develop illnesses like:
  a. Intrauterine infection
  b. Thrombocytopenia (low platelets level)
  c. Pneumonia (inflammation of air sacs in the lungs)
  d. CNS manifestations
  e. Hepatomegaly (enlarged liver)
  f. Chorioretinitis (inflammation of the uveal tract in the eye)

Symptoms include:

- Fever, for two weeks or more
- Generalised symptoms
- Cervical lymphadenopathy (lymph nodes enlargement)

Diagnosis

- Using the PCR
- We differentiate between CMV and EPV using serology tests and the antibodies produced against each virus. In both CMV and EPV infections we detect atypical lymphocytes in the blood.
- Using the serologic diagnosis, the presence of IgM antibodies indicates a present infection, while the presence of IgG antibodies indicates a previous infection , just like EPV.

Now keep in mind, if a mother was already infected (past infection/IgG antibodies) and the virus is dormant, it is **less likely** that she will transmit the infection to the fetus than if she had a primary infection.

Treatment

- Treatment for immunocompromised patients and neonates is very important. They're normally given "acyclovir" which is very efficient for them.

Roseola Virus (HHV6 & 7)

General Information

- HHV-6&7 are the main cause (HHV-6 more common though) of "Roseola" or childhood exanthem disease (the sixth disease) .
  Roseola: eruptive skin rash associated with fever
  The exanthema diseases are
  1.Measles (first disease) 2.Scarlet fever (second disease)
  3.German measles (third disease) 4.Variant of scarlet fever
  5.Erythema infectiosum 6.Roseola which is caused by HHV 6B
- Human herpesvirus 6 has two variants, variant a & b.
  - HHV-6**b** is the main cause of the early childhood infection.

Epidemiology

- Prevalence is high, almost 90% of people get infected during their childhood.

Transmission

- Usually through the saliva
- The virus infects many tissues and it can be found in saliva, GI tract, the lungs...etc. but the manifestations appear only on the skin.

Tropism

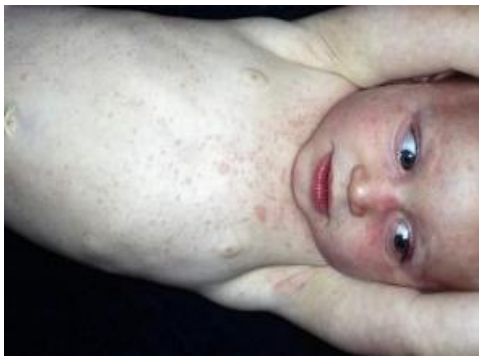
- HHV-6 infects mononuclear cells in the blood.
- Both viruses infect a very large number of cells.
  Justification: The main receptor for HHV-6 is CD46 and for HHV-7 is CD4, which are found on the surface of **many** cells.

Latency

- Occurs in the mononuclear cells in the blood and the reactivation is yet to be known or understood.

Clinical Features and Symptoms

- Adults or even children **older than 2** years don't normally get infected, most people have been infected when they were younger than 2.
- some people have subclinical infection with no symptoms.
- Immunocompromised patients might get infected if they weren't before, and it will cause an illness that is similar in symptoms to that of CMV (IMN symptoms)
- The infection is linked to diseases like pneumonitis, CNS manifestations, HIV.
- Roseola symptoms (most of the infections are symptomatic):
    a. High grade fever (above 39.4) which causes febrile seizure, or febrile illness (fever of an unknown cause)
    b. Upper respiratory tract symptoms
    c. Diarrhea
    d. The most characteristic symptom is the appearance of very small rose-like skin rash almost in 30% of the symptomatic cases.



- Some people develop all the symptoms except the rash so they wouldn't even know that they were infected by this virus.
- It is thought that this disease is associated with **multiple sclerosis** (an autoimmune disease), this assumption was made because in around 20% of the cases they found antibodies for EPV and HHV-6.
  (The doctor said that he doesn't believe this correlation but there might be an association because of the production of these antibodies (autoimmune diseases have many causes and the factors may be genetic, infectious... etc.) this association isn't proved YET.

Diagnosis

- Virus isolation is the best way to diagnose it.

Treatment

- The management of the disease depends on the symptoms.

Kaposi Sarcoma-associated Herpes Virus (HHV8/KSHV)

General Information

- The association between HHV and KS virus was discovered in 1994.
- Subfamily: Gamma herpes virinae.
- Genus: *Rhadinovirus*
- After 1981, the interest in this virus increased; because they found that these cases are related to **HIV**, and younger individuals, most of them are male homosexuals (in which the infection is very severe aggressive).
- At least 4 genotypes have been identified
    1. African endemic, especially in children
    2. Classic Mediterranean, that affect older individuals
    3. Epidemic form, which is the AIDS associated KS which is the most common
    4. Iatrogenic (wasn't mentioned)

Epidemiology

- The prevalence depends on the geographic area, ex:
  -Africa ➔ very high around 50%.
  -Europe or USA ➔ less than 10%.
- Male homosexuals are at higher risk of getting infected (the Prevalence is around 50%)
- It is mostly related to family practices, sexual behaviour.
- known to affect elderly Mediterranean people (80 or 90 years old).

Transmission

- oral fluids (saliva)
- The semen
- In some cases, it's transmitted vertically from a mother to her child via breastmilk.
- Homosexual practices

Tropism

- It infects B cells mainly.

Clinical Features and Symptoms

- The primary infection in **non-AIDS patients** is mostly **asymptomatic**, it might cause a febrile illness especially the African endemic .
- it is considered an AIDS defining Disease (list of illnesses associated with aids and used worldwide as a guideline for aids diagnosis).
- Manifestations occur in different places (skin, lungs, stomach, gums) and are: **slightly elevated, irregular in shape reddish/brown lesions** on the mouth or/and the throat, face. *can be life threatening*.
- Histopathology of the lesions is characterised by:
  presence of spindle shape cells of mesenchymal origin .
- **Kaposi's sarcoma** is the most common/ important disease associated with HHV8.
- Other rare diseases due to HHV8 are:
  a. **Multicentric castleman disease**
     - b cell hyperplasia in the germinal centres and lymph nodes.
     - causes systemic manifestations like: fever, fatigue, and plasmacytosis.
     - affects mainly HIV infected individuals**.**
  b. **primary effusion lymphoma** (an aggressive lymph cancer in body cavities)

Diagnosis

- It depends mostly on the histopathological examination .
- Hybridization techniques (of the DNA or RNA).
- qualitative PCR .
- For immunologic purposes we use the target method

Treatment

- It depends on the treatment of the underlying condition, for example highly active antiretroviral therapy (used to suppress the HIV virus) causes regression in some lesions.

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