Lectures 7/8: 05 December 2023

Herpesviruses

Malik Sallam, MD, PhD

The virus family *Herpesviridae* has 8 members that can cause human disease:

1. Human herpes virus 1 (herpes simplex virus type 1) حمو فيروسي غالباً في الفم
2. Human herpes virus 2 (herpes simplex virus type 2) حمو تناسلي
3. Human herpes virus 3 (varicella zoster virus) جدري الماء والحزام الناري
4. Human herpes virus 4 (Epstein Barr virus) الحمى الغُدية وبعض السرطانات الليمفاوية
5. Human herpes virus 5 (cytomegalovirus) الحمى الغدية وأمراض عند ذوي المناعة الخلوية الضعيفة
6. Human herpes virus 6 الطفح الوردي في الأطفال
7. Human herpes virus 7 الطفح الوردي في الأطفال
8. Human herpes virus 8 (Kaposi's sarcoma-associated herpesvirus) ورم خبيث في الأوعية الدموية

THE MOST IMPORTANT FEATURE: ALL herpesviruses establish lifelong persistent latent infection in the body, with periodic reactivation that can be asymptomatic or symptomatic especially if cellular immunity is suppressed.

عند دخول جميع الفيروسات المنتمية لعائلة الهيربس إلى الجسم فإنها تبقى إلى الأبد في الجسم ولن تخرج منه أبداً. ستبقى في غالب الأحيان كامنة بدون أعراض ولكنها قد تنشط في بعض الأحيان خاصةً إذا ما حدث نقص في المناعة الخلوية

Structure

Enveloped with double-stranded DNA genome.

Classification

HHV-1, HHV-2 and HHV-3 are alphaherpesvirinae viruses

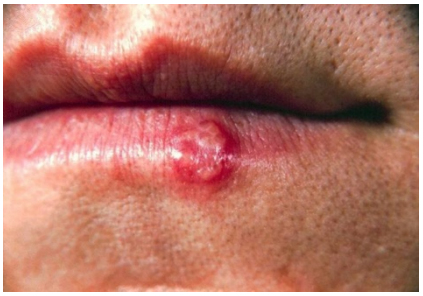
HHV-5, HHV-6 and HHV-7 are betaherpesvirinae viruses

HHV-4 and HHV-8 are gammaherpesvirinae viruses

Human herpes viruses 1 and 2 (herpes simplex virus types 1 and 2) HSV-1 and HSV-2:

Transmission: Direct contact, saliva, sexual, vertical.

Pathogenesis and clinical features: After contact, the virus infects the skin and mucous membranes causing the skin lesions (macules which are small flat lesions, that will evolve into papules which are small raised lesions that will develop into vesicles which are small raised lesions filled with clear fluid التي يُطلق عليها حويصلات followed by opening of the vesicles to form ulcers والتي يُطلق عليها تقرحات followed by crusting). The skin lesions last about 1–2 weeks, followed by complete recovery. The lesions can be extremely painful.

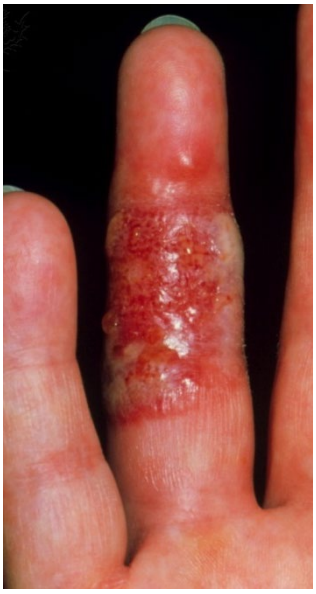


Important Note: This is the only material required for the exam in addition to the following textbook: Jawetz, Melnick, & Adelberg's Medical Microbiology

For any questions you can contact me through the following email: malik.sallam@ju.edu.jo

During this primary infection, the virus enters the sensory nerve endings and is transported by retrograde axonal transport into the dorsal (posterior) root ganglia (nuclei of sensory neurons) and the virus will establish latency there for life. During latency, **NO** active replication of the virus occurs. So, there is no production of virus proteins and the immune system cannot see the virus. Certain triggers can cause activation of the latent virus to cause reactivation. These triggers include stress, fever, and suppressed cellular immunity. On reactivation, the virus will move by anterograde axonal transport into the skin and mucous membranes to cause lesions similar to primary infection. A majority of primary and reactivation cases are **asymptomatic**.

Common sites of latency are the trigeminal nerve ganglia for HSV-1 and the sacral ganglia for HSV-2.



Diseases:

Gingivostomatitis.

Pharyngitis, tonsillitis.

Conjunctivitis (التهاب الطبقة الخارجية للعين والسطح الداخلي للجفن)

Keratitis (التهاب قرنية العين وهو التهاب خطير قد يؤدي للعمى)

Cold sores (fever blisters, herpes labialis)

Cutaneous herpes.

Herpetic whitlow (in the fingers).

Eczema herpeticum (in patients with allergic dermatitis).

Genital herpes.

Herpes encephalitis (infection of the brain tissue)

Herpes meningitis (infection affecting the meninges)

Neonatal herpes: Severe form with mortality of about 60%.

Disseminated severe disease in immunosuppressed patients (e.g., in AIDS patients).

Diagnosis:

Clinical.

PCR.

Antibodies: IgM in primary infection and IgG indicates past infection.

Nuclear inclusions in cells (technique called Tzanck smear).

Treatment:

Antivirals: acyclovir, valacyclovir, and vidarabine, all of which are inhibitors of viral DNA synthesis.

Important Note: This is the only material required for the exam in addition to the following textbook: Jawetz, Melnick, & Adelberg's Medical Microbiology

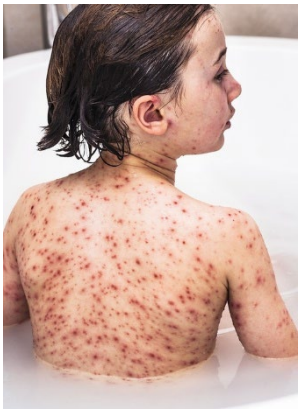
For any questions you can contact me through the following email: malik.sallam@ju.edu.jo

Prevention: Vaccines have not been approved for prevention so far.

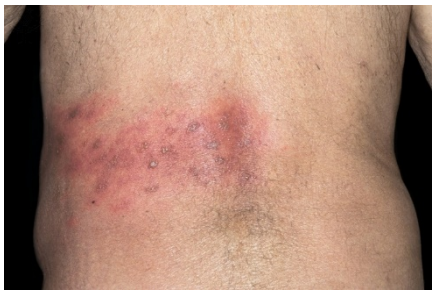
Epidemiology: In young adults, more than 90% have already been infected by HSV-1. Much lower prevalence of HSV-2 has been reported due to its sexual spread.

Human herpes virus 3 (varicella zoster virus) VZV

Transmission: Direct contact, aerosols.



Pathogenesis and clinical features: For primary infection (chickenpox, varicella, جدري الماء), after access into the upper respiratory tract, local replication occurs, followed by spread into the blood (primary viremia), followed by replication in the liver and spleen, followed by spread from the blood (secondary viremia) into the skin to give rise to chickenpox skin rash which is highly pruritic, itchy (تتسبب بحكّة شديدة). Similar to HSV-1 and HSV-2, VZV establish latency in dorsal root ganglia.



Upon reactivation, VZV cause lesions in one or a few skin segments innervated by the dorsal root ganglia. These lesions are called zoster or shingles (الحزام الناري). Reactivation occurs in older individuals and in case of immune suppression. The lesions are extremely painful. Even after the lesions disappear, pain may continue for several months (called post-herpetic neuralgia).

VZV is highly infectious. After an incubation period of 2–3 weeks, the patient is very infectious. The patient is also infectious by the end of the incubation period.

Infection gives immunity from chickenpox. But if the patient was not infected before, and gets exposed to shingles, the individual will get chickenpox which is the primary infection. So, the source of primary infection (chickenpox) is from outside the body, while the source of shingles is internal (latent VZV).

Complications of chickenpox can occur including pneumonia and meningitis. However, mortality is very low (1/100,000, and slightly higher among adults). Neonatal VZV is severe with mortality of about 30%.

Diagnosis:

Clinical.

PCR.

Antibodies: IgM in primary infection and IgG indicates past infection.

Nuclear inclusions in cells (technique called Tzanck smear).

Important Note: This is the only material required for the exam in addition to the following textbook: Jawetz, Melnick, & Adelberg's Medical Microbiology

For any questions you can contact me through the following email: malik.sallam@ju.edu.jo

Treatment:

Chickenpox: symptomatic. Zoster: acyclovir, valacyclovir, and famciclovir can reduce the length and severity shingles. For postherpetic neuralgia: tricyclic antidepressants, gabapentin and pregabalin, opioids, tramadol, etc. بتاخدوها إن شاء الله في علم الأدوية

Prevention:

Live attenuated vaccine is available to prevent chickenpox.

Therapeutic vaccines are available to reduce the occurrence of zoster (both recombinant subunit and live attenuated vaccines).

Epidemiology:

In countries where vaccination is not offered (due to cost), a majority of children get infected. Zoster likelihood increase with age.

Epstein Barr virus (EBV)

Transmission: saliva. So, the primary infection by EBV is called "kissing disease".

Tropism: Epithelial cells and B lymphocytes. **Site of latency:** B lymphocytes.

Receptor: CD21 (complement receptor 2)

Clinical features: The majority of primary infections is asymptomatic especially in children. In adults, primary infection is called "infectious mononucleosis".

Infectious mononucleosis = Fever + pharyngitis + cervical lymphadenopathy (تضخم العقد الليمفاوية في العنق)

Other features of infectious mononucleosis: fatigue, headache, splenomegaly.

Since EBV is an oncovirus, it has been linked the following cancers:

A. Burkitt lymphoma
B. Nasopharyngeal carcinoma
C. Hodgkin and non-Hodgkin lymphomas
D. Gastric carcinoma

Other disease linked to EBV infection in AIDS patients: **oral hairy leukoplakia**, which is a BENIGN wart-like growth that on the tongue. ورم حميد على لسان مرضى الإيدز

Diagnosis:

A. Clinical.
B. Blood film showing atypical lymphocytes (large reactive T cells).
C. PCR.
D. Serology: IgM to viral capsid antigen (VCA) in primary infection and IgG to EBV nuclear antigen (EBNA) indicates past infection.

Important Note: This is the only material required for the exam in addition to the following textbook: Jawetz, Melnick, & Adelberg's Medical Microbiology

For any questions you can contact me through the following email: malik.sallam@ju.edu.jo

Treatment:

EBV primary infection is a self-limited disease. Treatment is supportive.

Prevention: Vaccines have not been approved for prevention so far.

Epidemiology: In young adults, more than 90% have already been infected by EBV. In developing countries infection occurs in early childhood. In developed countries, infection occurs later in life at the beginning of sexual activities, kissing.

Cytomegalovirus (CMV)

Transmission: saliva, direct contact, mother-to-child

Tropism: *many many many cells.* ***Site of latency:*** *many many many cells.* ***Receptor:*** *many many many receptors.*

Clinical features: The majority of primary infections is asymptomatic especially in children. In adults, primary infection is called "infectious mononucleosis-like syndrome".

Infectious mononucleosis = Fever + pharyngitis + cervical lymphadenopathy (تضخم العقد الليمفاوية في العنق)

Other causes of infectious mononucleosis-like syndrome: EBV, herpes simplex viruses.

Other Diseases:

A. The importance of CMV reactivation is among **immunosuppressed patients** (for example in AIDS patients). It can cause: Pneumonia, gastroenteritis, retinitis (التهاب شبكية العين)
B. Congenital infection: CMV is the most common cause of **congenital infection**. Congenital CMV infection can result in deafness, blindness, mental retardation (تخلف عقلي)

Diagnosis:

A. Clinical (primary infection is mostly asymptomatic)
B. Blood film showing atypical lymphocytes (large reactive T cells).
C. PCR.
D. Serology: IgM in primary infection and IgG to indicates past infection.

Treatment:

CMV primary infection is a self-limited disease. Treatment is supportive.

In immunocompromised patients and in congenital infection: Ganciclovir (antiviral drug) is used.

Prevention: Vaccines have not been approved for prevention so far.

Important Note: This is the only material required for the exam in addition to the following textbook: Jawetz, Melnick, & Adelberg's Medical Microbiology

For any questions you can contact me through the following email: malik.sallam@ju.edu.jo

Epidemiology: In young adults, more than 90% have already been infected by CMV.

Roseola viruses (HHV-6 and HHV-7)

Transmission: saliva.

Clinical features: infection is usually acquired in the first year of life (in infants). The disease is called roseola infantum (exanthema subitum or sixth disease). The disease is characterized by **high fever and skin rash**. Importance of latency and reactivation is not known

Diagnosis:

A. Clinical
B. PCR

Treatment:

Supportive. Antipyretics خافض حرارة

Prevention: Vaccines have not been approved for prevention so far.

Epidemiology: In children, more than 90% have already been infected.

Kaposi sarcoma herpesvirus (HHV-8)

Transmission: saliva, sexual especially among male homosexuals, mother-to-child transmission.

Clinical features: Primary infection is asymptomatic. In AIDS patients, or in the elderly Kaposi sarcoma can occur (cancer of the blood and lymph vessels). It appears on the skin or mucous membranes.

Diagnosis:

A. Histopathology
B. PCR

Prevention: Vaccines have not been approved for prevention so far.

Epidemiology: The prevalence is low in the general population. The prevalence is high among male homosexuals.