Human Herpes Viruses

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- To know the clinically important HHVs.
- To know the common characteristics of HHVs.
- To know the common modes of transmission of different HHVs
- To know the clinical features of these infections, diagnostic methods and treatment.

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References:
Slides+Davidson+ microbiology Lippincott +master the board

Human Herpes Virus(HHV)

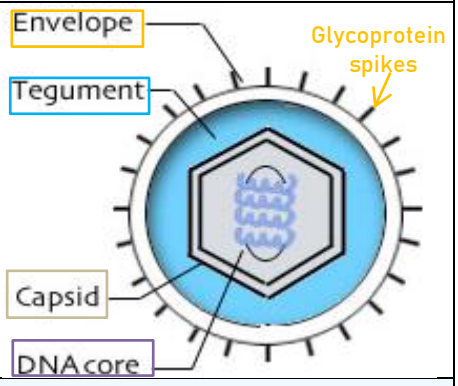
Overview of Human Herpes Virus(HHV)

Types of HHVs:	Common Characteristics:
- Herpes Simplex Virus type1 (HSV-1) - Herpes Simplex Virus type2 (HSV-2) - Varicella Zoster Virus (VZV) - Cytomegalovirus (CMV) - Epstein-Barr Virus (EBV) - Human Herpes Virus 6 (HHS-6) - Human Herpes Virus 7 (HHS-7) - Human Herpes Virus 8 (HHS-8)	- All DNA viruses . - All Encapsulated. - All Have **latency** after the initial infection. Which stay in the body forever - mostly Require close contact for transmission. - Human is the only reservoir.

Structure:

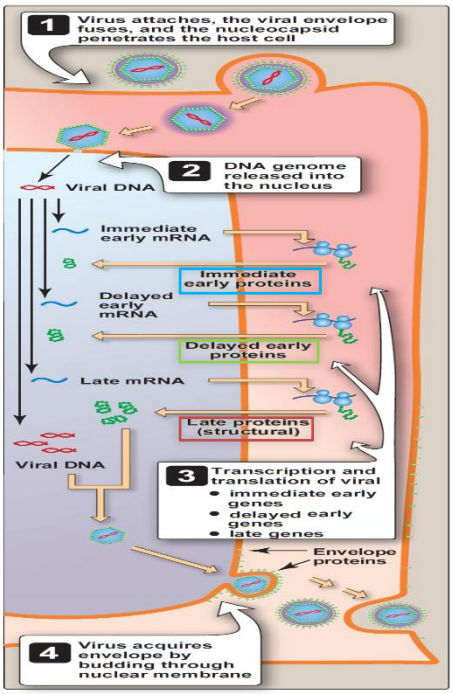
Herpesviruses have a unique four-layered structure:

- A core containing the large double-stranded DNA genome
- Genome is enclosed by an icosahedral capsid which is composed of capsomers.
- The capsid is surrounded by an amorphous[1] protein coat called the tegument(Between the envelope and the capsid).
- It is encased in a glycoprotein-bearing lipid bilayer envelope(envelope derived from the host's nuclear membrane).

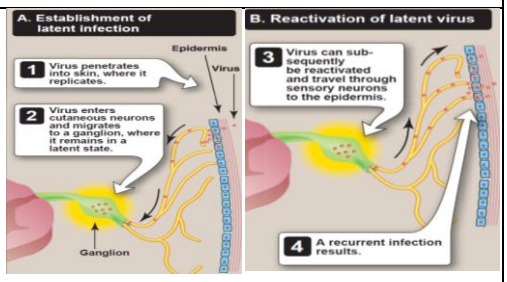
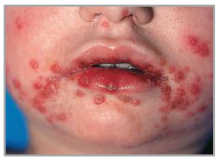
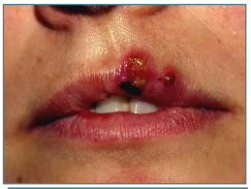
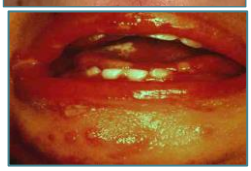
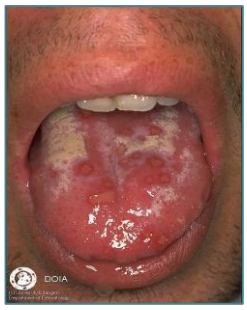
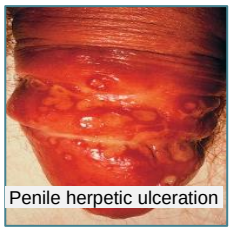
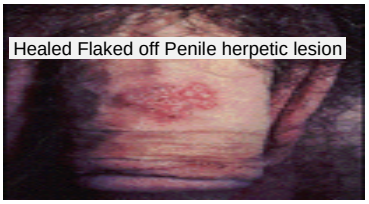


Replication:

→ Once the virus enters the host cell it goes directly to the nucleus
→ Upon entry into the host cell nucleus, three distinct phases of gene transcription and protein synthesis are initiated producing the **immediate-early**, **early**, and **late proteins**.
→ Viral nucleocapsid assembly occurs within the host cell nucleus.
→ The virus acquires its final envelope by budding into cytoplasmic vesicles



[1] without a clearly defined shape

<table>
<tr><th>Virus</th><th>HSV 1</th><th>HSV 2</th></tr>
<tr><td>Transmission:</td><td colspan="2">Transmission of both HSV types is by direct contact with virus-containing secretions or with lesions on mucosal or cutaneous surfaces.so u don't easily get infection</td></tr>
<tr><td rowspan="3">Characteristics:</td><td colspan="2">both viruses can cause either genital or oral lesions BUT:</td></tr>
<tr><td>- HSV-1 typically associated with lesions of the <u>oropharynx</u> (non-sexual contact) mostly over oral area</td><td>- HSV-2 typically associated with lesions of the <u>genitalia</u> (sexual contact)</td></tr>
<tr><td>- HSV-1 more commonly associated with meningoencephalitis</td><td>- HSV-2 known to cause Neonatal infection (vertical transmission at time of delivery) is associated with congenital malformations, intrauterine growth retardation (IUGR), chorioamnionitis (AKA intra-amniotic infection), and even neonatal death.</td></tr>
<tr><td colspan="3">both of them can cause Primary disease as well as Recurrent infections</td></tr>
<tr><td>Pathophysiology:</td><td colspan="2">1- Exposure to HSV at mucosal surfaces or abraded skin sites →permits entry of the virus and initiation of its replication in cells of the epidermis and dermis
2- After initial infection the virus infect the sensory and autonomic nerves and become dormant in the ganglion <u>(latent infection)</u>
  </td></tr>
<tr><td></td><td>Of trigeminal nerve for HSV-1(that's why its reactivation within the distribution of trigeminal nerve)</td><td>Of sacral route for HSV-2(that why it causes recurrent genital disease) .</td></tr>
<tr><td>Clinical features of primary infection</td><td>primary infection is usually asymptomatic and unnoticed, but When <u>symptomatic primary infection</u> is associated with:
- systemic manifestations (e.g., fevers, malaise)
- as well as oral lesions:
o Oral lesions involve groups of vesicles on patches of erythematous skin
o pharyngitis & Gingivostomatitis ↓ are the most frequent clinical manifestations of <u>first-episode</u> HSV-1 infection.
 
✓ HSV Gingivostomatitis is illness of children (preschool age)
▸NON-GENITAL HSV-1(Gingivostomatitis):
 
 
  </td><td>more severe and prolonged symptoms, lasting up to 3 weeks:
- Very painful genital vesicles or pustules
- Other findings are tender inguinal lymphadenopathy and vaginal and/or urethral discharge ,myalgias,itching, and dysuria and other symptoms of UTI especially in women.
- Constitutional symptoms (e.g., fever, headache, malaise) often present in primary infection.
▸ GENITAL HSV-2:
 
 
 
▸ Notes:
24 hrs before the lesion appear the pt is infectious, and once the lesion started to flake off here's the pt become noninfectious</td></tr>
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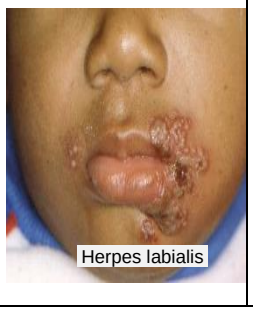
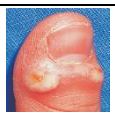
<tr><td>Clinical features of recurrent infection</td><td>Recurrent attacks occur throughout life, most often in association with concomitant medical illness, menstruation, mechanical trauma, immunosuppression, psychological stress or, for oral lesions, UV light exposure

Recurrent herpes labialis(mcq?) ‘cold sore’ is the most frequent clinical manifestation of reactivation HSV infection,the most common reason for people with HSV-1 infection to seek medical attention is recurrent attacks of herpes labialis

▸ Important Note:
Herpes labialis is quite characteristic of HSV1 no other dis can cause this except HSV1 ,this pic shows severe dis which’s affecting lip line & also can affect the tongue with vesicles

 
Herpes labialis

Recurrent HSV genital disease is a common cause of recurrent painful ulceration

inoculation lesion on the finger gives rise to a paronychia termed a ‘whitlow’→ in contacts of patients with herpetic lesions. It was formerly seen in health-care workers and dentists, but is prevented by protective gloves.
 
HSV-1 is the cause in 60% of cases of herpetic whitlow, and HSV-2 is the cause in the remaining 40%</td></tr>
<tr><td>Investigations:</td><td>1- can be made clinically when characteristic lesions are recognized.the classical clinical pic is straightforward to diagnose it

2- Serology(the most common way to diagnose it)diagnostic test:Direct fluorescent assay and ELISA
○ sensitivity 80%
○ Results available within minutes to hoursblood serology looking for IgG & IgM level ,IgM tells u if there acute infection
3- Viral culture :by swabbing the base of the ulcer, viral culture only available in research lab not even available in most of labs setting
4- Cytology:looking for cytopathic effect
5- PCR:if there skin lesion take a biopsy and send it for PCR but more commonly if u suspect meningoencephalitis send CSF for PCR to give u the result</td></tr>
<tr><td>Treatment:</td><td>- FIRST LINE: Acyclovir(PO,IV,topical)
- Alternative to acyclovir:
○ Penciclovir topical
○ Famciclovir PO given twice daily and not approved for immunocompromised pt
○ Valacyclovir PO given twice daily and not approved for immunocompromised pt

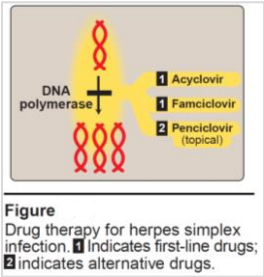
 

Figure
Drug therapy for herpes simplex infection. 1 Indicates first-line drugs; 2 indicates alternative drugs.

▸ Notes:
✓ No cure available , antiviral medication will only relief symptoms and reduces the duration .
✓ Route, dose, duration depends on clinical picture(severity of the dis)and whether immunocompromised or competent,for example:
○ PO acyclovir, may be given as prophylaxis for patients with frequent recurrences.
○ IV acyclovir: for severe diseases like meningoencephalitis
○ topical acyclovir: for mild dis like oral labialis
*prolonged treatment for 21 days in immunocompromised while only for 5 days in immunocompetent</td></tr>
</table>

Varicella Zoster Virus (VZV)

Characteristics:

- Primary infection : Chickenpox
- Recurrent infection : Herpes zoster (shingles)

Patho-physiology:

→ The virus is spread by the respiratory route (airborne and contact) and replicates in the nasopharynx or upper respiratory tract.

→ Followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and, ultimately, viremia.(that's why chicken pox pt develop systemic rash affecting all the body)

→ then after 10 days The virus establishes latency within the dorsal root ganglia(where stays here forever and once it reactivates will cause shingles) .

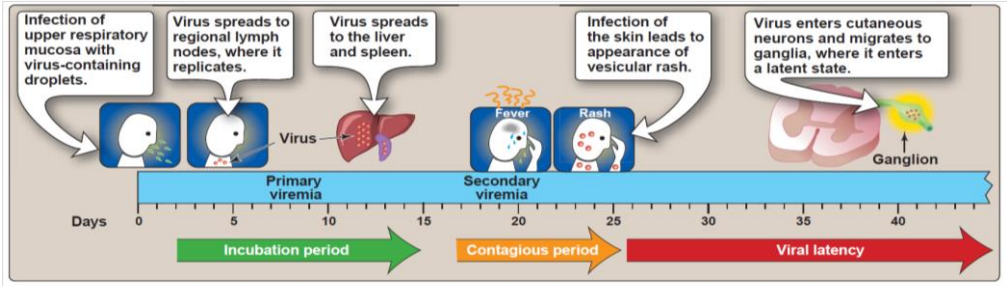
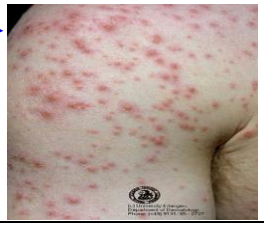


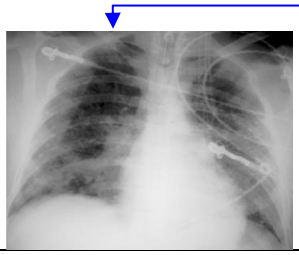
Figure 25.10
Time course of varicella (chickenpox) in children. In adults, the disease shows a longer time course and is more severe.

Clinical features of chicken pox

Overall, chickenpox is a disease of childhood, because 90% of cases occur in children younger than 13 years of age. nowadays it be come uncommon due to vaccination

vesicular lesions affecting all part of the body





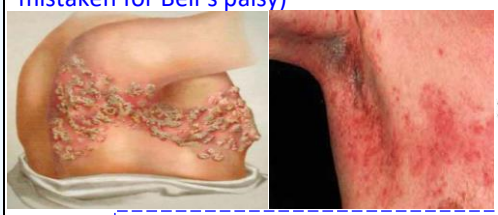
one known complication of chickenpox is super bacterial pneumonia , severe dis require hospitalization and iv antibiotics

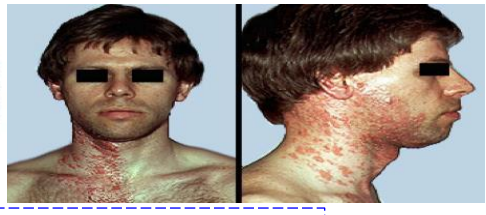
Clinical features of Herpes zoster (shingles)

Reactivation of VZV leads to VZ:

it's affecting specific dermatomal site ,thoracic dermatomes are most commonly involved,only seen in one side(UNILATERAL) which is pretty characteristic and straight forward for diagnosing of VZV infection.

shingle can also cause severe disease in which the ophthalmic division of the trigeminal nerve is affected; vesicles may appear on the cornea and lead to ulceration. This condition
can lead to blindness and urgent ophthalmology review is required. shingle also can affect any of cranial nerve including the facial nerve causes the Ramsay Hunt syndrome of facial palsy it's medical emergency (This may be mistaken for Bell's palsy)





▶ **NOTICE:**the rash for shingles is very similar to HSV1 in which it's vesicular ,so the way to differentiate between all these disease is the location of these vesicular rash

Investigations:

1- Clinical picture is typical straightforward to diagnose the virus
2- Serology similar to HSV ,is what really we depends on.
3- Viral culture not really available
4- PCR ,by taking skin biopsy ,or csf biopsy if u suspect meningoencephalitis which is very rare with ZVZ

Treatment:

similar to HSV:Acyclovir or\Valacyclovir or\Famciclovir

Prevention:

- VZV vaccination.
- VZV immunoglobulin (VZIG)passive immunity: given to whom nonimmune(not vaccinated yet or didn't get previous infection) and at risk to develop chickenpox .
- If admitted need airborne infection isolation and contact precautions (BUT whose have a positive history of varicella and/or a positive VZ antibody do not need PPE 'Personal protective equipment')

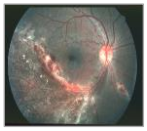
Cytomegalovirus (CMV)

Characteristics:

- Worldwide distribution Australia is the least;The largest virus that infects human beings
- Latency after primary infection
- Infection ranges from asymptomatic to severe multisystemic disease

Clinical features:

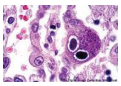
- Primary infection:
  - most commonly Asymptomatic
  - Infectious mononucleosis syndrome clinically identical to that caused by EBV. It is estimated that about 8 percent of infectious mononucleosis (IM) cases are caused by CMV. Persistent fever, muscle pain, and lymphadenopathy are characteristic IM symptoms, as are elevated levels of abnormal lymphocytes and liver enzymes.
- Secondary infections exclusively seen in Immunocompromised patients(AIDS & hematopoietic stem cell transplant):
  - Pneumonitis
  - Retinitis especially AIDS pt→
  - Colitis
  - Multisystem



Investigations:

Diagnosis almost always depends on laboratory confirmation and cannot be made on clinical grounds alone.

- **Serologic tests:**(antigen detection from the blood),Serological tests can identify latent (IgG) or primary (IgM)simple detection of anti-HCMV antibody is not generally useful Because the incidence of HCMV infection in the population is so high, and periodic inapparent recurrent infections occur frequently.
- **PCR:** most commonly used
- **Viral cultures**: from blood ,urine*,tissue. (slowly growing) NOT routinely done
- **Histology:** The virus can also be identified in tissues by the presence of characteristic intranuclear 'owl's eye' inclusions (see the fig→)



*Detection of CMV in urine is not helpful in diagnosing infection, except in neonates, since CMV is intermittently shed in the urine throughout life following infection(Davidson)

▶ **Notes:** Atypical lymphocytosis is not as prominent as in EBV

Treatment:

- ganciclovir
- foscarnet or cidofovir: used in rare cases of UL97 & UL54 mutation who are resistant to ganciclovir therapy

Epstein-Barr Virus (EBV)

Characteristics:

- Ubiquitous human herpes virus.
- By adulthood 90 to 95% of most populations are positive.
- Mostly causes asymptomatic infections.
- Carcinogenic: Strong association with African Burkitt's lymphoma &Nasopharyngeal carcinoma.

Transmission:

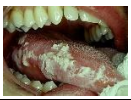
- Spread occurs by intimate contact between susceptible individuals and asymptomatic shedders of EBV(that's why it called kissing dis).

Clinical features:

- Infectious mononucleosis, symptoms include:
  - Fever
  - Sore throat
  - Lymphadenopathy →

▶ **Notes:** The major distinguishing feature of HCMV IM is the absence of the heterophile antibodies that characterize IM caused by EBV

- With AIDS pt oral hairy leucoplakia: presenting as a pale, ridged lesion on the side of the tongue→



Investigations:

- **Serologic**(antibodies testing):
  - Transient appearance of **heterophile antibodies(♀diagnostic test)**(which is detected by the Paul–Bunnell or 'Monospot' tes) 70–92% sensitivity and 96–100% specificity(heterophile AB is weak antibodies produced by non specific B cells)
  - later on, Permanent emergence of antibodies to EB
- **Hematologic Findings:**
  - >50% mononuclear cells hint for EBV
  - Lymphocytosis(>10% atypical lymphocytes hint for EBV)
  - neutropenia
  - thrombocytopenia
  - EBV specific antibodies
- **after serology u can do PCR** as supportive diagnostic test

Treatment:

- Treatment of infectious mononucleosis is largely supportive because more than 95% of the patients recover uneventfully without specific therapy,there's no antiviral therapy for EBV
- Corticosteroids(for pt with severe infectious mononucleosis with obstructive sx of their pharynx or larynx)

Summary

From Doctor's Slides:

Virus	Infection
HSV Type 1	- Herpes labialis ('cold sores') - Keratoconjunctivitis - Finger infections ('whitlows') - Encephalitis - Primary stomatitis - Genital infections
HSV Type 2	- Genital infections - Neonatal infection (acquired during vaginal delivery)
Varicella zoster virus (VZV)	- Chickenpox - Shingles (herpes zoster)

Cytomegalovirus (CMV)	- Congenital infection
	- Disease in immunocompromised patients:
	  ○ Pneumonitis
	  ○ Retinitis
	  ○ Colitis
	  ○ systemic infection

Epstein-Barr virus (EBV)	- Infectious mononucleosis - Burkitt's lymphoma - Nasopharyngeal carcinoma - Oral hairy Cell leukoplakia (AIDS patients)
Human herpesvirus 6 (HHV-6) and 7 (HHV-7) Roseolovirus	- In children,Exanthem subitum (Roseola): three day fever - Disease in immunocompromised patients
Human herpesvirus 8 (HHV-8)	- Associated with Kaposi's sarcoma

Take Home Massage:
- Herpes virus Primary infection with herpes simplex virus causes genital and oral ulceration, and systemic infection. - Varicella zoster occurs at any stage of HIV infection, but may be more aggressive and longer lasting than in immunocompetent patients. Treatment is with acyclovir. - Human herpesvirus 8 is associated with Kaposi's sarcoma. - EBV causes oral hairy leucoplakia, presenting as a pale, ridged lesion on the side of the tongue. EBV is also associated with primary cerebral lymphoma and non-Hodgkin's lymphoma

MCQs

SAQs

Taken From Doctor's Slides

1) A 16 year old came with fever and sore throat, his blood film showed 50% mononuclear cells and 20% atypical lymphocytes. What's the cause of his condition?

a. Coronavirus
b. EBV Sample
c. Influenza Virus
d. CMV

2) A 50 years old diabetic male presented with painful vesicular lesions that spread over a band encircling the left side of his chest?

a. Acyclovir
b. Gancovir
c. Foscarnet
d. Cidofovir

3)A 22 year old bed bound man after a RTA was brought to ED with SOB and was diagnosed as acute asthma exacerbation and treated with salbutamol and IV steroids. 24 hours later he developed rash around mouth and ear. What drug should be given at the time?

a. Acyclovir
b. Imatinib
c. Vancomycin

4)Which one of the following is the cause of Kaposi sarcoma?

a. HIV
b. HHV8
c. EBV
d. CMV

5)Which one of the following presents with a rash in all the developmental stages?

a. Chicken pox
b. Measles
c. Rubella
d. Rift Valley hemorrhagic fever

6)A 55 year old man, had kidney transplantation 3 years ago, presents to the hospital complaining of severe sharp pain along the left chest for 2 days. The pain extending from the middle thorax in the back and extending along the left side up to the nipple. On examination he was found to have erythematous rash with some vesicular lesion in the same site of the pain.
Most likely this rash is due to :

a. Dermatitis secondary to skin contact with a chemical gent
b. Direct contact with a patient who has viral infection
c. Reactivation of an old virus that was dormant in the dorsal nerve root ganglion
d. Reactivation of an old fungal infection that was dormant in the skin

1)36y\o Indian professor presents to ID clinic with recurrent oral vesicular lesions that lasts for 10 to 14 days,4 to 5 lesion around his lip, slightly painful, interferes with his lecturing, No fever, no oral cavity lesions,Gets these episodes almost on a monthly basis, Previously diagnosed with HSV-1, took acyclovir on occasion with good results Brought on occasionally with stress,You recommend ?Chronic suppressive therapy with acyclovir

2) 32y\o 40 weeks pregnant lady who is in labour,OB found her to have genital vesicular lesions suspected to be HSV-2,She had similar genital lesions twice in the past 4 years,You recommend:

- C-Section if possible
- IV acyclovir till delivery
- Refer baby to neonatal ID once born

Answer key:

1 (B) | 2 (A) | 3 (A) | 4 (B) | 5 (A) | 6 (C)|