Lecture outline: HERPES VIRUSES 12.02.2016

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HERPES VIRUSES

Ds DNA linear genome,
Icosohedral nuclear capsid,
Enveloped - ether sensitive
180 - 200 nm size

(Refer: EM picture of herpesvirus particles)

Intra nuclear replication

HHV-1 (HSV -1)	herpes simplex type -1
HHV-2 (HSV-2)	herpes simplex type-2
HHV-3 (VZV)	varicella zoster virus
HHV-4 (EBV)	Epstein - Bar virus
HHV-5 (HCMV)	human cytomegalo virus
HHV-6	(human herpes virus -6)
HHV-7	(human herpes virus -7)
HHV-8	(human herpes virus –8/KSHV)

Alpha herpes virus	HSV -1
	HSV -2
	VZV
Beta herpes virus	CMV
	HHV 6
	HHV 7
Gamma herpes virus	EBV
	HHV 8

Properties:-

(1) Herpes viruses have the ability to establish latent infections in neurons lymphocytes.
(2) Produce characteristic eosinophilic intranuclear inclusion bodies.
(3) Following the latent infection the viruses can reactivate and, subsequently produce recurrent diseases.
(4) Primary infection is more severe than recurrences in general.
(5) More severe in adolescence or adult life than in childhood.
(6) Low socio economic groups virus circulate freely & infects early in life (Mild infection). High socio economic groups infects during adolescence / adults leading to severe infection

Herpesviruses

Classification: Herpesviridae (Family)

Herpesvirus (Genus)

Herpes simplex type 1 / type 2 (Species)

Herpes simplex virus (HSV)

Causes wide variety of infections in humans.
Two types (HSV 1& 2) share Ag that makes serological diagnosis difficult.
Can be distinguished antigenically by monoclonal Abs.
In healthy persons virus infects oral cavity or genital tract
HSV -1 upper part of the body common
HSV -2 genital lesions
There are exceptions to the rule.
Recurrent HSV 1 & 2 infections occur even in the presence of high Ab titers.

Herpes simplex type 1 (HSV – 1)

- Infection by this type is common.
- Most common in upper parts of body.

Primary HSV-1 infection:-

- Acute ulcerative gingivostomatitis characterized by vesicles in gums, cheeks, tongue
- Vesicles become ulcerated later.
- Children also develop lymphadenopathy
- Some times in children, infection may passed unnoticed.

Exposure to type 1 begins in childhood with 25-50% Ab develop in college students.
(Sri Lankan data: 50% in children, >76% in adults)
Type 1 from genital site may be auto inoculation with oral secretions.
Following primary infection patients recover from the disease.
But virus become latent in trigeminal ganglion (sensory neurons).
Reactivate to cause lesions referred to *COLD SORES (Herpes labialis)*

COLD SORES (Herpes labialis)
Painful, burning and itching lesions.
Crops of vesicles appear at mucocutaneous junctions of mouth, nostrils.

Dangerous form is reactivation from ophthalmic branch of 5th Nerve leading to severe kerato-conjunctivitis and visual impairment

Factors bringing about recurrences

1. Sunlight
2. Menstruation
3. Fever (usually malaria)
4. Meningococcal & respiratory infections (pneumonia)
5. Allergic reactions
6. Stress
7. Common cold

* During reactivation virus descends along the sensory nerves. Produce disease in the area supplied by the nerve.

Herpes simplex type 1 (HSV – 1)

HSV -2 also causes primary infections & recurrent infections
Lesions are in relation to genitalia. Exception is Neonatal infection.

- 1/3 isolates from genital tract due to HSV-1
- 2/3 isolates from genital tract due to HSV-2
- Type-2 : very few isolates from oral cavity

Exposure to type 2 does not begin until the teens and continues throughout the period of sexual activity
(Sri Lankan data: 5% in Children, 8% in 15-19 yrs and 26% in 60-64yrs: Sunil-Chandra et al 2001)

Isolation of type-2 from genital sites implies sexual transmission

Typing of herpes isolates from genital tract is a valuable prognostic information.
Type-2 genital infection id more likely to recur than type-1
HSV-2 causes painful vesicular eruptions

Lesions in the female involve:
Labia, vagina and cervix and causes vulvo-vaginitis
Cervix acts as a reservoir of infection..

Lesions in the Male involve:
Glans & shaft of the penis causes balanitis

Transmission:

In general,

- Poor hygienic conditions & overcrowding --- young children.
- Better hygienic conditions ---- young adults
- Source of HSV 1 in a family is a parent with a recurrent infection
- HSV 1 is transmitted by Orally (saliva or eating or drinking utensils)
- HSV 2 is transmitted by 1. Sexually, 2. Maternal infection to baby at birth (perinatal) and 3. Congenital infection

HSV 2 infection in the pregnant female

1. During pregnancy (Primary infection);

Vertical transmission leads to congenital infection.

2. *At the time of delivery (primary/recurrent infection);*

Virus transmits to child at birth (through the birth canal) (Perinatal transmission)

Congenital HSV infection

Rarely occur *in-utero*.

When pregnant mother get disease for the 1st time & no Abs.

Fetus affected born with -vesicular eruptions
- jaundice
- hepatosplenomegaly
- thrombocytopenic purpura

- If mother is symptomatic - lesions should be cultured
  - Delivery by Cesarean

If asymptomatic & no vaginal lesions - vaginal delivery OK

Disease conditions due to Herpes simplex virus infections.

1. Encephalitis, aseptic meningitis & meningo-encephalitis.
2. Herpetic whitlow
3. Eczema herpeticum
4. Herpes gladiatorum/scrum pox
5. Pharyngitis usually primary infections.
6. Tonsillitis ulcerated mucosa limited to posterior pharynx.
7. Haemorrhagic cystitis part of disseminated infection.
8. Herpetic proctitis may occur in homosexual men

Herpes simplex virus encephalitis

Neonatal form

following primary & generalized infection in infancy.

Adult form

probably due to virus reactivation in Trigeminal ganglia (prompt Acyclovir treatment).

HSV infections in immunocompromised persons

- oesophagitis
- tracheobronchitis
- pneumonia
- disseminated infection
- hepatitis

HSV eye infections

* Herpetic keratitis (Dendritic ulcer)
* Conjunctivitis

Source of eye infections:
Primary (childhood), Recurrent. Transfer from cold sore
or Lab. Accidents

1. Conjunctivits accompanied by fever, photophobia and regional lymphadenopathy
2. Herpetic keratitis (Dendritic ulcer)
   - Branching or dendritic appearance.
   - Common cause of corneal blindness.
   - Reactivation in ophthalmic division of trigeminal nerve.

Neonatal HSV infections

Source:

Cold sore of attending adults
Herpetic whitlow
Perinatal
congenital (disseminated infection)

Frequently fatal - If disease limited to nose, eyes and mouth no fatality
Diagnose by vesicular lesions (may be absent in 20%)

Poor prognostic factors
-DIC
-generalised disease
-comatose state
-prematurity

Important to diagnose maternal infection because Neonatal infection can be prevented by cesarean section.

Diagnosis of HSV

1. Scrapings from vesicles onto a glass slide lab
    1. Light Microscopy for infected cells (giant cells & intranuclear inclusion bodies)
    2. Immunoflourescence staining using specific antiserum.
2. ELISA to detect virus antigen.
3. Swabs from vesicles in transport media inoculate to tissue culture. Diagnosis based on CPE by 24 hrs.

5. CF test or Neutralization.
    Positive in primary infections
    Recurrent - infections no rise in Ab

Antiviral therapy

(Inactive) (active)
ACV → ACV-MP+P → ACV-TP
(Herpes virus TK) inhibition of viral DNA polymerase enzyme
↓
incorporation into viral DNA
↓
Chain termination

Varicella Zoster virus

Highly infectious
Disease forms 1. Chicken pox (Varicella)
2. Zoster (Shingles) (Herpes zoster)

Chicken pox (varicella) is the primary infection by VZV

Highly infectious

- Mainly/commonly affect children under 10yrs age
- Adults develop more severe illness
- Patients of leukaemi severe or even fatal immunocompromised
- Incubation period 14-21days

Transmission & spread

1. Droplets from upper respiratory tract (oropharynx)
2. Discharge from ruptured lesions (skin)
3. Through contact with herpes zoster

Route of entry : upper respiratory tract

Clinical features
1st sign of disease is rash
1st lesions on palate before the rash
2nd day of illness rash on Trunk (spots max. density) & Face
Limbs (spots sparse)

Rash
Macules appear 1st →within few hours --→ Vesicular -→-within 24 hours→Pustular
Pustules are damage (rupture) by scratching & itch
If unruptured →Dry in few days → scabs

Spots
Appear in crops.
Lesions at all stages of development at any area at the same time.
Considerable discomfort to healthy people.
Symptoms mild & brief.
May produce pneumonia.
Immunocompromised people it causes life threatening disseminated infection
Following primary infection virus remain latent in sensory ganglia of the spinal cord (for many years)
Then it reactivate & produce disease resembles chicken pox but limited to the dermatome.
This disease condition is called Shingles or Herpes zoster

Rash comparison

Chicken pox	Small pox
1. Trunk, neck, face & proximal parts of limbs	1.Mainly peripheral distal points of limbs & neck
2. Leaves a scab	2. Leaves a scab
3. Rash appear in crops	3. Lesions at same stages
4. Does not leave scars	4. Leave scars

Complications of Chicken pox
1. Direct viral effects Pneumonia

2. Post viral effects—myocarditis, encephalitis and glomerulonephritis
3. Secondary bacterial infection of the skin -→ septicaemia
→osteomyelitis/septic arthritis
4. Intrauterine infection→ Congenital limb defects

Herpes zoster / Shingles
- Localized lesion
- Unilateral
- One or few dermatomes affected
- Lesion does not extend beyond midline
- Seen mainly in adults who had varicella before
- From a shingles patient chicken pox can be contracted
- Reactivation - may be spontaneous usually adults elderly or middle age
  - Immunosuppressed (i.e. AIDS, Malignancy)

About 20 % of those people who have had chicken pox will get zoster at some time during their lives. Most people will get zoster only once.
Read: Prodromal signs & symptoms

Complications of Shingles

1. Ophthalmic herpes
2. Segmented muscle wasting
3. CNS infection myelitis
   encephalitis
4. Herpetic neuralgia
5. Ramsay-Hunt Syndrome

Diagnosis of VZV infection

Before small pox was eradicated, it was important to differentiate between chicken pox and small pox

1. EM on scrapings of vesicles

Scrapings from a vesicle Examine under EM;

Chicken pox

Icosohedral enveloped virus.

Small pox

Brick shaped large complex virus.

2. Biopsy - light microscope intranuclear inclusion bodies

Biopsy specimen is Stained & Examine under light microscope

Chicken pox intranuclear inclusion bodies (herpes virus).
Small pox intra cytoplasmic inclusion bodies.

3. Tissue culture

By growing on tissue culture chicken pox can be diagnosed.

4. Gel precipitation with anti VZV serum on vesicle fluid

Virological and immunological basis for the Management:

(a). Varicella

Majority need no to treatment
ACV (Acyclovir) is given to immunocompromised patients
Secondary infections skin antiseptic (chlorhexidine) & antibiotics
Immunocompromised children in contact with Varicella & Shingles are indicated treatment with Human antivaricella gammaglobulin (zoster immunoglobulin)

(b). Shingles

Oral ACV if started early
Systemic ACV for immunosuppressed persons

Prevention

Live attenuated VZV vaccine

1. Children below 13 years: - one dose
2. Over 13 years age: - 2 doses 1-2 months apart

CMV (Cytomegalovirus)

Common virus - >60% population has Abs

Has ability to produce latent infection & recurrent infection

Virus can be isolated from
- -saliva
- -urine
- -tears
- -respiratory infections
- -semen (from WBC fraction)

Transmission

- -person to person (unknown)
- -blood transfusion
- -organ transplant
- -venereal transmission
- -congenital

CMV from mother → placenta → pass to offspring
- Cervical secretions
- breast milk

(A). Clinical types & diseases caused by (CMV)

1. Congenital infection
   - -hepatosplenomegaly
   - -purpura
   - -encephalitis
2. Neonatal infection.
3. Heterophil Ab negative IM.
4. Hepatitis (rare).
5. Pneumonia in immunosuppressed patients.
   (common in cardiac transplant & renal transplant)
6. Destructive retinitis in <u>immunosuppressed</u> patients.
7. Enteritis in <u>immunosuppressed</u> patients.

(B) Asymptomatic infection

<u>Congenital infection</u>

Disease is known as Cytomegalic inclusion disease of the newborn.

>90% women in Asia & Africa are seropositive

<u>Primary maternal infection</u>

40% cases → congenital infection of fetuses
- 95% of them are asymptomatic. No long term consequence
- 5% show signs at birth

Recurrent maternal disease

20% cases → congenital infection in seropositive mother
fetal damage uncommon

Symptoms of Congenital CMV

Jaundice
Hepatosplenomegaly
Purpuric rash
Haemolytic anaemia
Microcephaly
Hearing defects
Chorio-retinitis
Cerebral calcification → Neurological complications (spasticity)
Survivals → mental retardation

Mental retardation, Spasticity, Eye abnormalities, Hearing defects (deafness) may not be detected until later in life

Virus invade foetus

1. When immunity decreases in mother while she is pregnant (re-infection)
2. Recurrences in mother during pregnancy
3. Primary infection (No Ab) of mother in pregnancy

Acquired infection

1. Infant may get from an outside host
2. From mother by birth canal
3. Adult are infeted → Asymptomatic &
50% cases of IM (negative Paul Bunnel test)

Diagnosis

1. Biopsy - most children with cytomegalic inclusion body disease have characteristic "owl eye" cells.

Examine cells microscopically. Large swollen cells with intranuclear inclusion bodies dark coloured with pale halo surrounding.

CMV lung - Microscopy & histology:

Cytomegalic inclusion in the infected pnuemocytes characterized by enlarged nucleus with a round and discrete intranuclear inclusion surrounded by a white halo

2. Centrifuged deposit of urine - owl eye cells may be seen
3. Saliva, CSF or Throat swab can be inoculate onto human fibroblast cells
   Look for 'owl eye' cells.
4. CMV specific IgM in serum by CFT for > 4 fold titre

Treatment for CMV infection

- Gangcyclovir for disseminated CMV & CMV retinitis in AIDS ACV not effective

Epstein-Barr virus (EBV)

- Primary cause of infectious mononucleosis (IM) (Glandular fever)
- Acute self limited infection
- Isolated 1st from an African Burkitt's lymphoma
- >90% population has Ab

Primary infection

Developing countries very early in childhood & acquire from mother

- Young children asymptomatic or minimally symptomatic
- Adolescents (developed countries)→50% develop IM (IgM in serum)
- EBV is not the only cause of IM
- When it is by EBV, it is --- +ve for Paul Bunnel test
  ----- EBV IgM +ve

Pathogenesis of EBV

Virus (via saliva) → infect pharyngeal epithelium (productive replication) → Virus excretion via saliva

Productive replication pharyngeal epithelium → Infect circulating B cells →B cells get immortalized (Latent infection)

Polyclonal B cell proliferation induce Cell Mediated Immunity to infection leading to produce an array of Abs to many Ags (heterophil Abs)

Activated T cells causes to produce atypical lymphocytosis

Clinical features of infectious mononucleosis (Glandular fever)

EBV infection of young adults transmitted - oral contact (exchange of saliva)
Incubation period 7-10 days

Acute illness	Exudative tonsillitis
Malaise	Petechial rash on palate
Headache	Lymph gland enlargement
Abdominal discomfort	Splenomegaly
Anorexia	Maculopapular rash (rash common if
Fever	ampicillin given for sore throat)

Abnormal findings in lab tests

Atypical lymphocytosis
Positive monospot test (Paul Bunnell test)
Elevation of liver enzymes

Complications of IM

Chronic Fatigue Syndrome (common)
Hepatitis (rare)
Haemolytic anaemia (rare)
Thrombocytopenia (rare)
Rupture of spleen (rare)
Meningoencephalitis (rare)

Atypical lymphocytosis common in young.
Spread by saliva due to close personal contact (Kissing Disease)
Not highly infectious.
Reactivation usually not occur like other herpes viruses.

Immunosuppression
(i.e. HIV, Transplant)
Loss of regulatory T cell control and Develop EBVrelated tumors (Iry Brain lymphoma)

EBV associated malignancies
1. BL (Burkitt's lymphoma)
Tumory Jaw - endemic in central Africa. It is an aggressive B-cell lymphoma
2. NPC (Nasopharyngeal Carcinoma) common in China, Singapore, Hong Kong
In addition to EBV environmental co-factor + chromosomal translocation.

Lab. diagnosis
1.Peripheral blood culture
2.Serology Heterophile Ab test
Detection Ag: EBNA, LMP, EA, MA
3. Detection of genome on biopsies.

Human herpesvirus -6

Cause a very common childhood disease :

Exanthem subitum
(Roseola infantum)
(Duke disease)
(4th disease)
Worldwide
Children between 6 months - 3 years age.
Incubation period 2 weeks.
Acute febrile illness last for 3-4 days.
followed by a rash (maculo papular).

- Virus is present in saliva - 85% of adults.
- Virus replicate in T cells (CD4+)
- Shed in saliva.
- Virus can be isolated in patients with AIDS, Neoplastic disease & LPD

HHV-7

- Significance is not known.
- Seroconversion in most children.
- Later than in case of HHV-6.
- >75% adult saliva positive for virus.

HHV-8 (KSHV)

Karposis sarcoma (KS) is caused by HHV-8

- is now associated with AIDS.
- It is more frequently associated with AIDS in homosexual men than AIDS in IV drug users.
- Recent research has shown that this malignancy is caused by a newly discovered herpes virus, HHV 8.
- The malignancy results in purplish, grape-like lesions in the skin, gastrointestinal tract, and other organs