HERPES VIRUSES

HERPES VIRUSES

Ds DNA linear genome,

Icosohedral nuclear capsid,

Enveloped - ether sensitive

180 - 200 nm size

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

Gama herpes virus → EBV
HHV 8

Properties :-

(1) Herpes viruses ⇨ Have the ability to establish latent infections in neurons or 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 Gps → virus circulate freely & infects early in life. (Mild infection)

High socio economic Gps → Infects during adolescence / adults. (Severe infection)

HSV

- Causes wide variety of infections in humans.
- Two serotypes (HSV 1& 2)

share Ag that makes serological diagnosis difficult.
Can distinguish 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.

HSV - 1

- Infection by this type is common.
- Most common in upper parts of body.
- Most common age Gp → children age 2-4 yrs.

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 Sunil-Chandra et al 2001)
- Type 1 from genital site ➡ may be auto inoculation with oral secretions.

Cont..d.

- 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 SORE

- Painful, burning and itching lesions.
- Crops of vesicles appear at mucocutaneous junctions of mouth, nostrils.
- Dangerous form is reactivation from ophthalmic branch of 5^{th} Nerve

↓

Severe kerato-conjunctivitis

↓

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.

HSV-2

Causes → primary infections

→ recurrent infections

Lesions in relation to genitalia.

Exception → Neonatal infection.

- 1/3 isolates from genital tract → HSV-1
- 2/3 → HSV-2 from genital tract
- 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 ⟶ More likely to recur than type-1

HSV-2 causes painful vesicular eruptions

Lesions in the female involve

labia

vagina → vulvo-vaginitis

cervix

- Cervix acts as a reservoir of infection..

Lesions in the Male glans → Balanitis

→ shaft of the penis

Transmission

In general,

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

Indication for Cesarean section.

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
  - -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

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

Primary (childhood)

Recurrent

Transfer from cold sore

Lab. Accidents

1. Conjunctivits accompanied by
   - fever
   - photophobia
   - 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)

Cont..d.

- Frequently fatal
- If disease limited to
  - nose
  - eyes
  - 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.
- Neonatal infection prevented by cesarean section.

Diagnosis of HSV

1. Scrapings from vesicles onto a glass slide ⟶ lab ⟶ EM
2. Immunoflourescence staining using specific antiserum.
3. ELISA to detect virus antigen.
4. 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

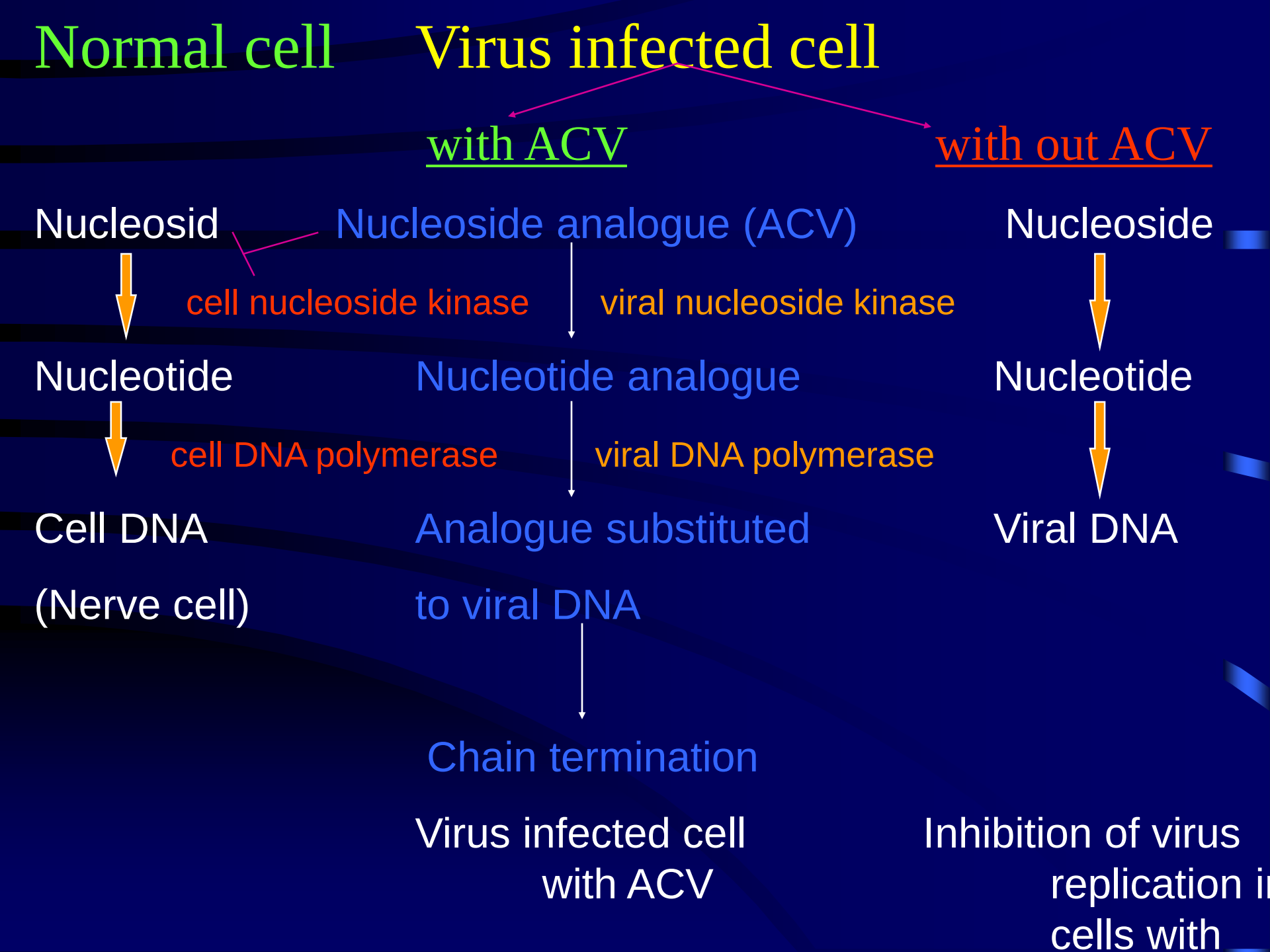
(Inactive) (active)

Herpes virus TK enzyme

inhibition of viral DNA polymerase

incorporation into viral DNA

Chain termination


Normal cell
Virus infected cell
with ACV
with out ACV
Nucleosid
Nucleoside analogue (ACV)
Nucleoside
cell nucleoside kinase
viral nucleoside kinase
Nucleotide
Nucleotide analogue
Nucleotide
cell DNA polymerase
viral DNA polymerase
Cell DNA
Analogue substituted
Viral DNA
(Nerve cell)
to viral DNA
Chain termination
Virus infected cell
with ACV
Inhibition of virus
replication i
cells with

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 → leukaemia → severe or even fatal
  → immunocompromised
- Incubation period → 14-21d

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 few hours

↓

Pustular → within 24 hours

- unruptured
- Damage by scratching & itch (rupture)

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 → life threatening disseminated infection

cont..d.

cont..d.

Following primary infection

↓

virus remain latent in sensory ganglia of the spinal cord

(for many years)

↓

reactivation & produce disease resembles chicken pox

but limited to the dermatome

Disease = 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
   - myocarditis
2. Post viral effects → encephalitis
   - glomerulonephritis
3. Secondary bacterial infection → 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 → AIDS, Malignancy

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

1. EM on scrapings of vesicles
2. Biopsy - light microscope ⟶ intranuclear inclusion bodies
3. Tissue culture
4. Gel precipitation with anti VZV serum on vesicle fluid

Diagnosis of VZV infection

Important to differentiate between → chicken pox
→ small pox

a) Scrapings from a vesicle

Examine under EM;

Chicken pox

Icosohedral enveloped virus.

Small pox

Brick shaped large complex virus.

b) Biopsy specimen

Stain

Examine under light microscope

Chicken pox → intranuclear inclusion bodies (herpes virus).

Small pox → intra cytoplasmic inclusion bodies.

c) Tissue culture

By growing on tissue culture chicken pox can be diagnosed.

cont..d.

Cont..d.

d) VZV & HSV differentiation

1. EM on vesicle fluid not helpful.
2. VZV

   - can be grown in human embryonic tissue.

   -does not produce pocks on chorio allantoic membrane of chick embryo.

3. Gel precipitation with anti VZV serum on vesicular fluid.

Management

Varicella

Majority no need to treat

ACV (Acyclovir) ⟶ immunocompromised patients

Secondary infections ⟷ skin antiseptic (chlorhexidine)

↘ antibiotics

Immunocompromised children in contact with Varicella & Shingles ⟶ Human antivaricella gammaglobulin (zoster immunoglobulin)

Shingles

Oral ACV if started early

Systemic ACV for immunosuppressed

Prevention

Live attenuated VZV vaccine

1. Children below 13 years: 0ne 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 → pass → offspring ← placenta

offspring ← cervical secretions

offspring ← breast milk

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

cont..d.

Cont..d.

6. Destructive retinitis in immunosuppressed patients.

7. Enteritis in immunosuppressed patients.

(B) Asymptomatic infection

Congenital infection

Cytomegalic inclusion disease of the newborn.

*>90% women in → Asia seropositive

→ Africa

Primary maternal infection

↓

40% cases → congenital infection of foetuses

→ 95% asymptomatic

→ 5% show signs at birth

↓

No long term sequalae

Recurrent maternal disease

↓

20% cases → congenital infection

↓

seropositive mother

foetal damage uncommon

Symptoms of Congenital CMV

Jaundice

Hepatosplenomegaly

Purpuric rash

Haemolytic anaemia

Microcephaly

Hearing defects

Chorio-retinitis

Cerebral calcification → Neurological complications (spasticity)

Cerebral calcification → 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 disease
   ↓
   have characteristic “owl eye” cells

   Examine cells → microscopically

   large swollen cells with intranuclear inclusion bodies
   dark coloured with pale halo surrounding.

2. Centrifuged deposit of urine → owl eye cells may be seen

3. Saliva

   CSF } inoculate onto human fibroblast cells
   ↓
   Throat swab } Look for ‘owl eye’ cells.

4. CMV specific IgM in serum by CFT

   > 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

<u>Primary infection</u>

- Developing countries → very early in childhood
  Acquire from mother

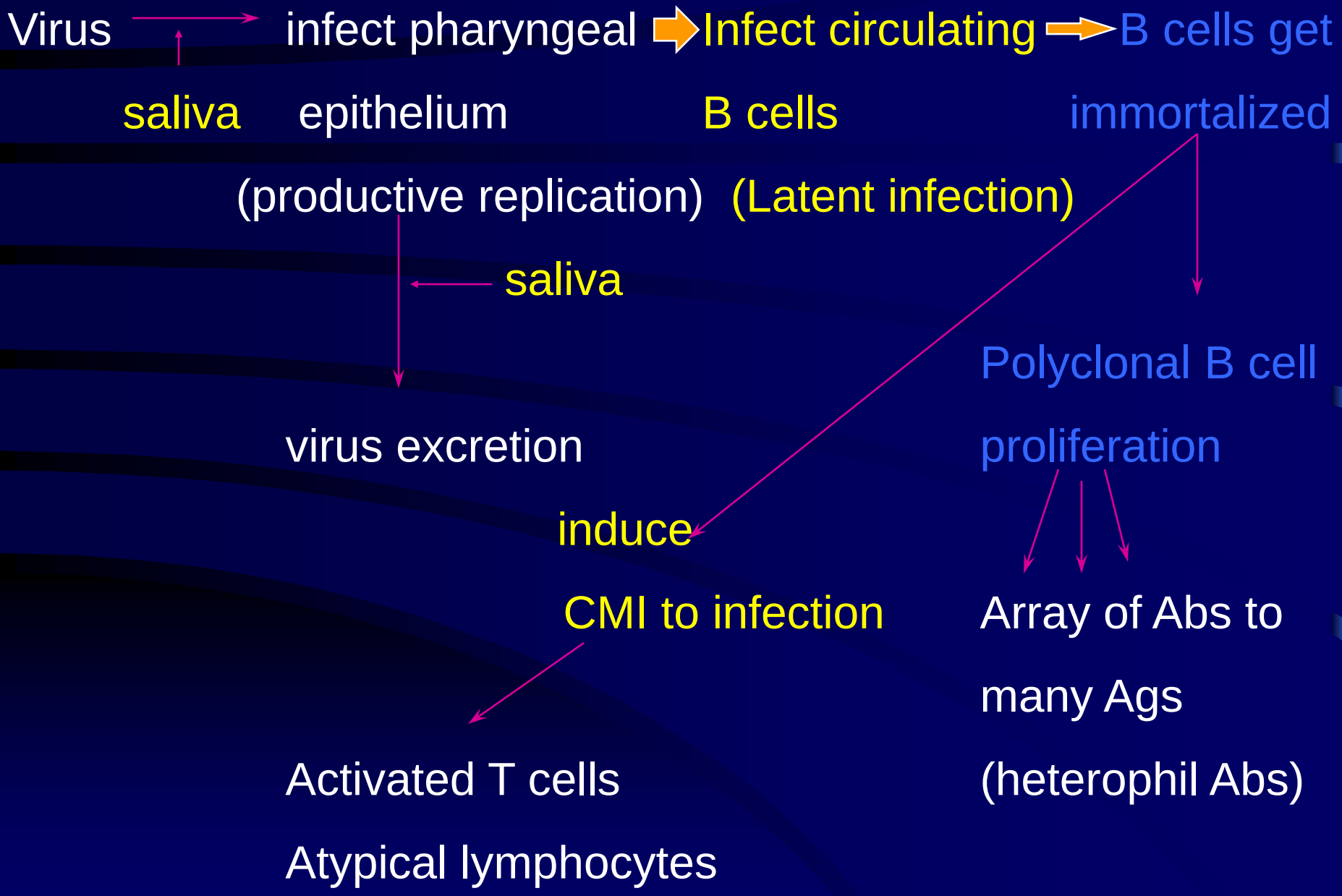
cont..d.

Cont..d.

- 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



EBV associated malignancies

1. BL (Burkitt's lymphoma)

   Tumory Jaw - endemic in central Africa

2. NPC (Nasopharyngeal Carcinoma)

   common in → China
   → Singapore
   → Hong Kong

In addition to EBV environmental co-factor + chromosomal translocation.

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

- Malaise
- Headache
- Abdominal discomfort
- Anorexia
- Fever

→

- Exudative tonsillitis
- Petechial rash on palate
- Lymph gland enlargement
- Splenomegaly
- Maculopapular rash (rash common if ampicillin given for sore throat)

Abnormal findings in lab tests

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

Complications

Chronic Fatigue Syndrome (common)

Hepatitis (rare)

Haemolytic anaemia (rare)

Thrombocytopenia (rare)

Rupture of spleen (rare)

Meningoencephalitis (rare)

Atypical lymphocytosis common in young.

Spread → saliva

close personal contact (Kissing Disease)

Not highly infectious.

Reactivation usually not occur like other herpes viruses.

Immunosuppression

HIV, Transplant → Loss of regulatory T cell control → Develop EBV related tumors (Iry Brain lymphoma)

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

HHV-8 (KSHV)

KS is common among AID patients.

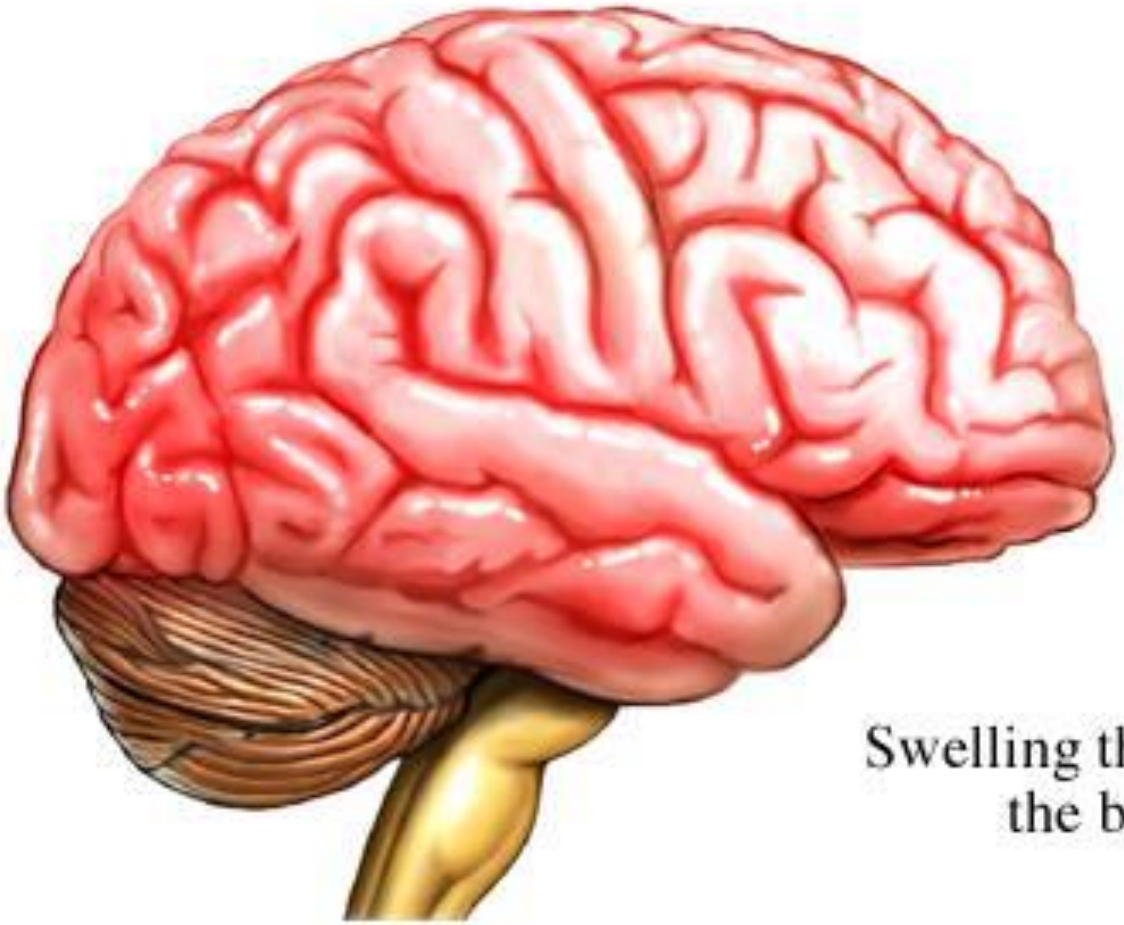
KS is caysed by HHV-8

Oral herpes.

Herpes simplex virus infection: oral herpes

Recurrent genital herpes of the mons venus

Genital-Herpes



Swelling throughout
the brain

Japanese encephalitis patient