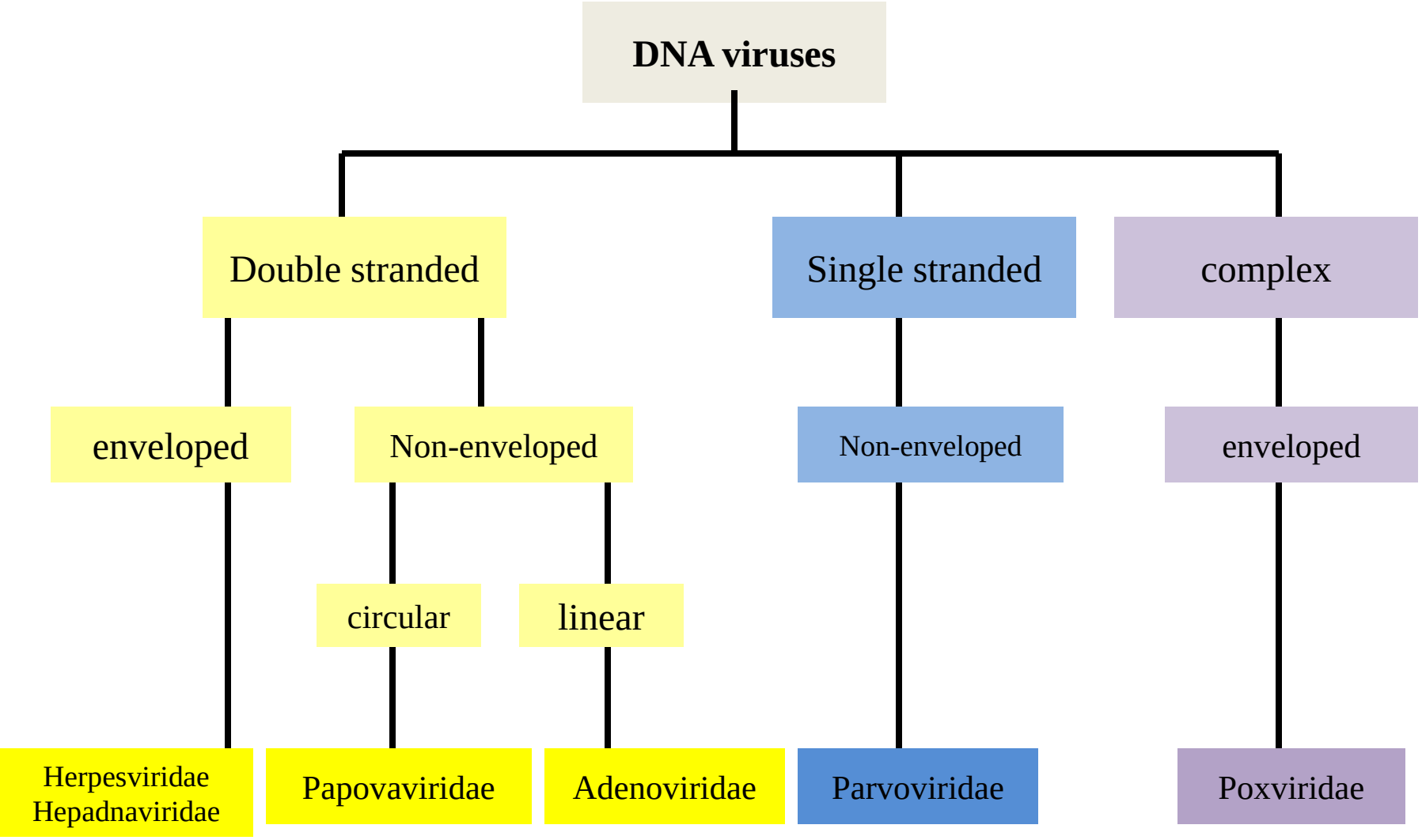
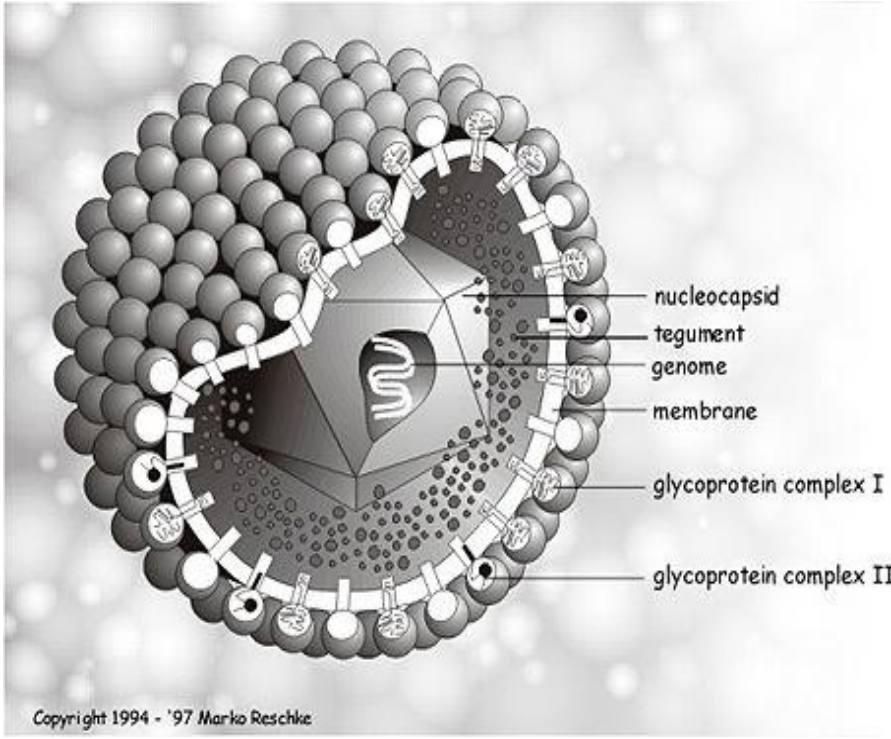
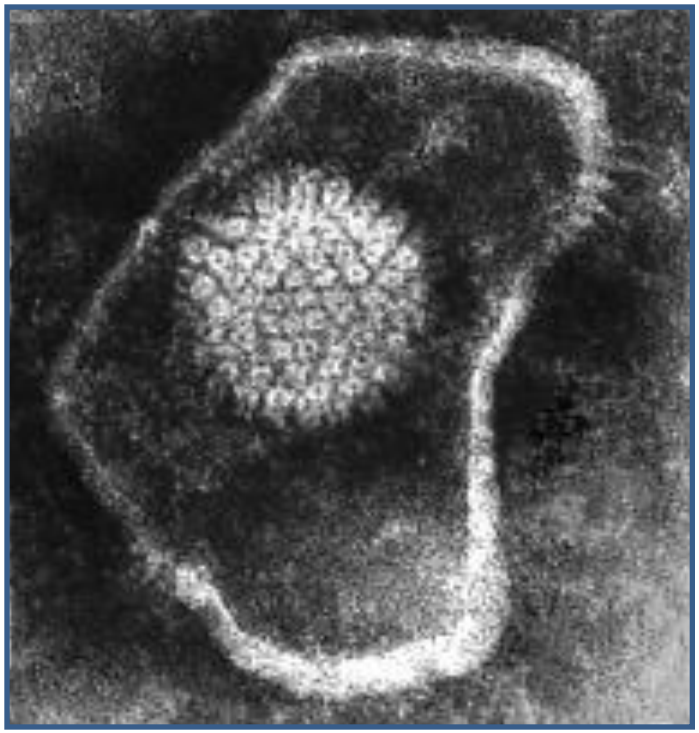
DNA VIRUSES


DNA viruses
Double stranded
Single stranded
complex
enveloped
Non-enveloped
Non-enveloped
enveloped
circular
linear
Herpesviridae
Hepadnaviridae
Papovaviridae
Adenoviridae
Parvoviridae
Poxviridae

herpesviruses

- **dsDNA , linear, enveloped, 180-200 nm**
- **Large genome, codes for 75 viral proteins**
- **50-70% similarity**
- **Cross reactivity between HSV and VZV**





HSV-2 virus particle. Note that all herpesviruses have identical morphology and cannot be distinguished from each other under electron microscopy.

- Three subfamilies:
  - Alphaherpesviruses - HSV-1, HSV-2, VZV
  - Betaherpesviruses - CMV, HHV-6, HHV-7
  - Gammaherpesviruses - EBV, HHV-8
- painfull skin ulcers, chickenpox, and encephalitis.
- Acute infection followed by latent infection
- Latent: virus genome present in the cell (episome), not integrated
- Reactivation gives recurrent disease
- Replication: receptor, heparan sulphate
- IE (proteins initiate and regulate transcription)
- E: non-structural proteins (DNA poly., TK)
- L: major structural proteins (capsid, spikes)
- role of TK, polymerase, in antiviral effect.
- Only 25% of DNA/protein produced incorborated into virions

- Recurrent ulcers in skin and mucosal membranes, above (HSV-1) and below (HSV-2) the waist, latency.
- Man is the only natural host for HSV. Direct contact with infected secretions 90% +ve abs for type1, type 2 sexually active 15-30%.
- Primary infection is usually trivial or subclinical in most individuals. It is a disease mainly of very young children ie. those below 5 years.
- Acute infection, multinucleated giant cells, latent infection of sensory and autonomic nerve ganglion.
- Following primary infection, 45% of orally infected individuals and 60% of patients with genital herpes will experience recurrences
- Latent infection: HSV-1, trigeminal, superior cervical and vagal nerve ganglion
- Reactivation: ultraviolet, sunlight, fever, excitement, emotional stress and trauma.
- HSV-2: sacral region S2,S3. Antivirals don't work.

Pathogenesis

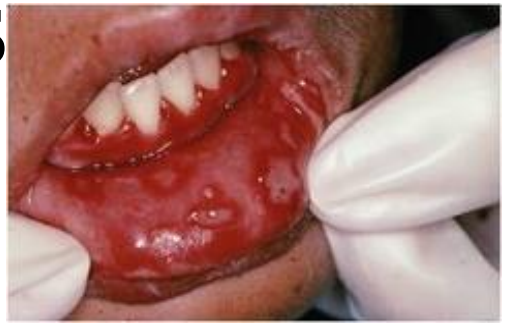
- During the primary infection, HSV spreads locally and a short-lived viraemia occurs, whereby the virus is disseminated in the body. Spread to the to craniospinal ganglia occurs.
- The virus then establishes latency in the craniospinal ganglia.
- The exact mechanism of latency is not known, it may be true latency where there is no viral replication or viral persistence where there is a low level of viral replication.
- Reactivation - It is well known that many triggers can provoke a recurrence. These include physical or psychological stress, infection; especially pneumococcal and meningococcal, fever, irradiation; including sunlight, and menstruation.

Clinical Manifestations

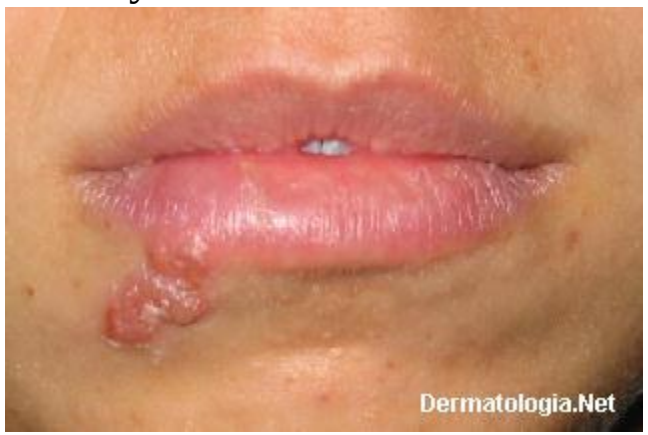
HSV is involved in a variety of clinical manifestations which includes ;-

1. Acute gingivostomatitis
2. Herpes Labialis (cold sore)
3. Ocular Herpes
4. Herpes Genitalis
5. Meningitis
6. Encephalitis
7. Neonatal herpes

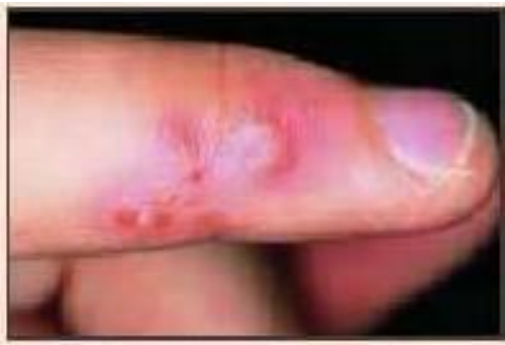
Oral-facial Herpes



- Acute Gingivostomatitis
  - Acute gingivostomatitis is the commonest manifestation of primary herpetic infection.
  - The patient experiences pain and bleeding of the gums. 1 - 8 mm ulcers with necrotic bases are present. Neck glands are commonly enlarged accompanied by fever.
  - Usually a self limiting disease which lasts from5-13 days.
- Herpes labialis (cold sore, fever blisters)
  - Following primary infection, 45% of orally infected individuals will experience reactivation. The actual frequency of recurrences varies widely between individuals.
  - Herpes labialis (cold sore) is a recurrence of oral HSV.
  - A prodrome of tingling, warmth or itching at the site usually heralds the recurrence. About 12 hours later, red-ness appears followed by papules and then vesicles. Last 1 week



- Herpetic whitlow
  - Infection of the finger or nail area through small cuts
  - Painful vesicular lesion of the finger then pustulates
  - Mimic bacterial paronychia



One or more small tender vesicles, typically on the distal phalanx, characterize herpes simplex infection of the fingers.

- Ocular herpes

HSV causes a broad spectrum of ocular disease, ranging from mild superficial lesions involving the external eye, to severe sight-threatening diseases of the inner eye. Diseases caused include the following:-

  - Primary HSV keratitis – dendritic ulcers
  - Recurrent HSV keratitis
  - HSV conjunctivitis
  - Iridocyclitis, chorioretinitis and cataract

Herpes Simplex Encephalitis

- Herpes Simplex encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:
- Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%.
- Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

Genital Herpes

- HSV-2 causes 70% of first episode genital HSV infections
- Genital lesions may be primary, recurrent. First episode can be years later and last 12 days.
- Many sites can be involved which includes the penis, vagina, cervix, anus, vulva, bladder, the sacral nerve routes, the spinal and the meninges.
- IP 5days.
- Lesion begin as small erythmatous papule, form vesicle then pustule. Lesions heal without scarring.
- Dysuria is a common complaint, in severe cases, there may be urinary retention. Inguinal lymph node involvement.
- Asymptomatic shedding may occur.

Neonatal Herpes Simplex

- The baby is usually infected perinatally during passage through the birth canal.
- Premature rupturing of the membranes is a well recognized risk factor.
- The spectrum of neonatal HSV infection varies from a mild disease localized to the skin to a fatal disseminated infection (MR 60%).
- Where dissemination occurs, the organs most commonly involved are the liver, adrenals and the brain.
- Where the brain is involved, the prognosis is particularly severe. The encephalitis is global and of such severity that the brain may be liquefied.
- A large proportion of survivors of neonatal HSV infection have residual disabilities.
- Acyclovir should be promptly given in all suspected cases of neonatal HSV infection.
- The only means of prevention is to offer caesarean section to mothers with florid genital HSV lesions.

Laboratory Diagnosis

- Tzanck test
  - Smear from base of lesion, stain Giemsa show internuclear inclusion
- Direct Detection
  - Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV
  - Immunofluorescence of skin scrappings - can distinguish between HSV and VZV
  - PCR - now used routinely for the diagnosis of herpes simple encephalitis
- Virus Isolation
  - HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days for a result to be available.
- Serology
  - Not that useful in the acute phase because it takes 1-2 weeks before antibodies appear after infection. Used to document recent infection.

Management

At present, there are only a few indications of antiviral chemo-therapy, with the high cost of antiviral drugs being a main consideration. Generally, antiviral chemotherapy is indicated where the primary infection is especially severe, where there is dissemination, where sight is threatened, and herpes simplex encephalitis.

- Acyclovir – this the drug of choice for most situations at present. It is available in a number of formulations:-
  - I.V. (HSV infection in normal and immunocompromised patients)
  - Oral (treatment and long term suppression of mucocutaneous herpes and prophylaxis of HSV in immunocompromised patients)
  - Cream (HSV infection of the skin and mucous membranes)
  - Ophthalmic ointment
- Famciclovir and valacyclovir – oral only, more expensive than acyclovir.

- Safe sexual practices
- C-section

Varicella- Zoster Virus

Properties

- Belong to the alphaherpesvirus subfamily of herpesviruses
- Double stranded DNA enveloped virus
- One antigenic serotype only, although there is some cross reaction with HSV.
- Winter and spring months
- IP 11-21 days
- Major mode of transmission respiratory. Contact with lesion
- Communicability 2days before, 3-4 days into the rash

Epidemiology

- Primary varicella is an endemic disease. Varicella is one of the classic diseases of childhood, with the highest prevalence occurring in the 4 - 10 years old age group.
- Varicella is highly communicable, with an attack rate of 90% in close contacts.
- Most people (90%) become infected before adulthood but 10% of young adults remain susceptible.
- Herpes zoster, in contrast, occurs sporadically and evenly throughout the year.

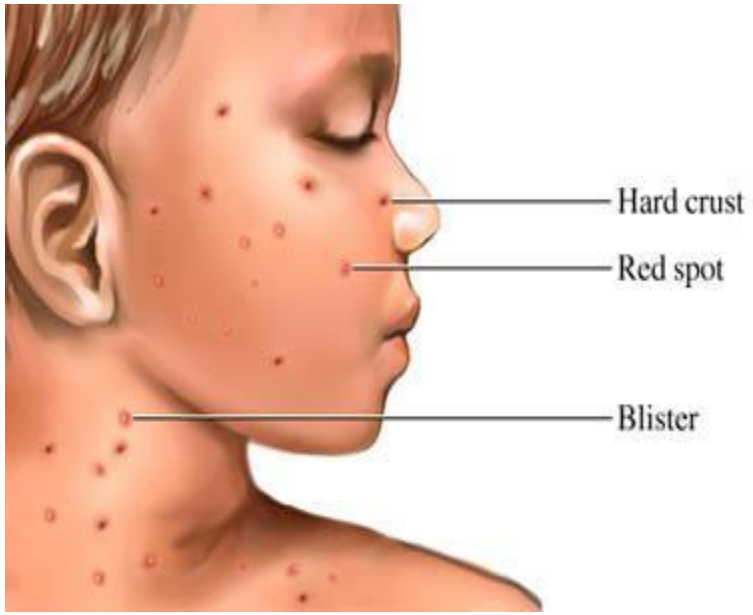
Pathogenesis

- The virus is thought to gain entry via the respiratory tract and spreads shortly after to the lymphoid system.
- After an incubation period of 14 days, the virus arrives at its main target organ, the skin.
- URTI, LNs, viremia, RES, viremia, skin.
- Following the primary infection, the virus remains latent in the cerebral or posterior root ganglia. In 10 - 20% of individuals, a single recurrent infection occurs after several decades.
- The virus reactivates in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve, producing a varicella form rash in the distribution of a dermatome.

Varicella

- Primary infection results in varicella (chickenpox)
- Incubation period of 14-21 days
- Presents fever, lymphadadenopathy. a widespread vesicular rash.
- The features are so characteristic that a diagnosis can usually be made on clinical grounds alone.
- Complications are rare but occurs more frequently and with greater severity in adults and immunocompromised patients.
- Most common complication is secondary bacterial infection of the vesicles.
- Severe complications which may be life threatening include viral pneumonia, encephalititis, and haemorrhagic chickenpox.

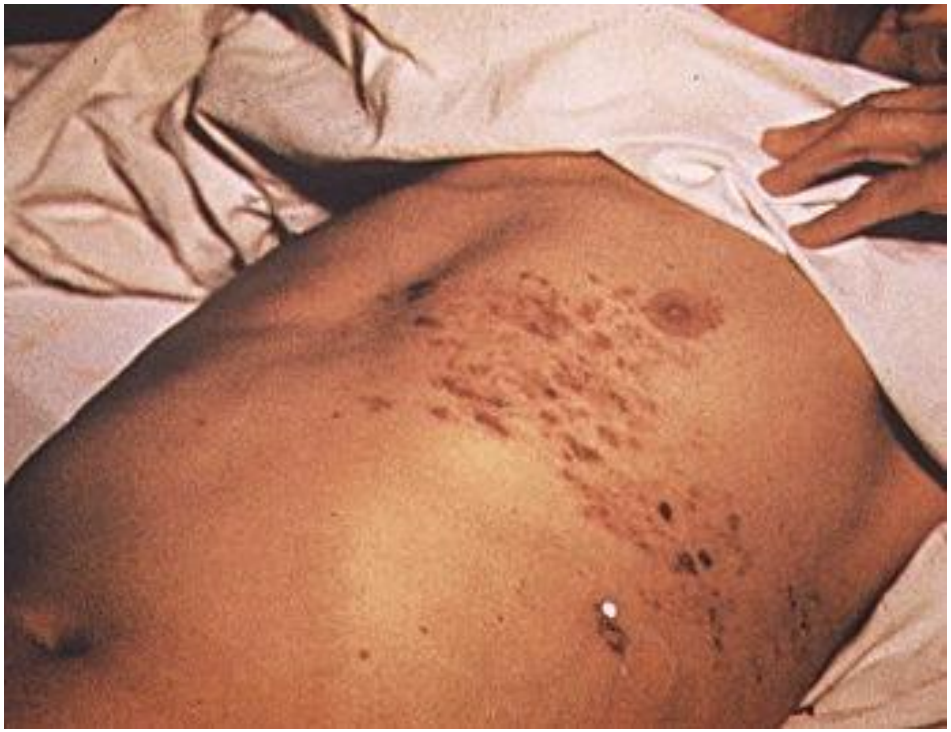
Rash of Chickenpox

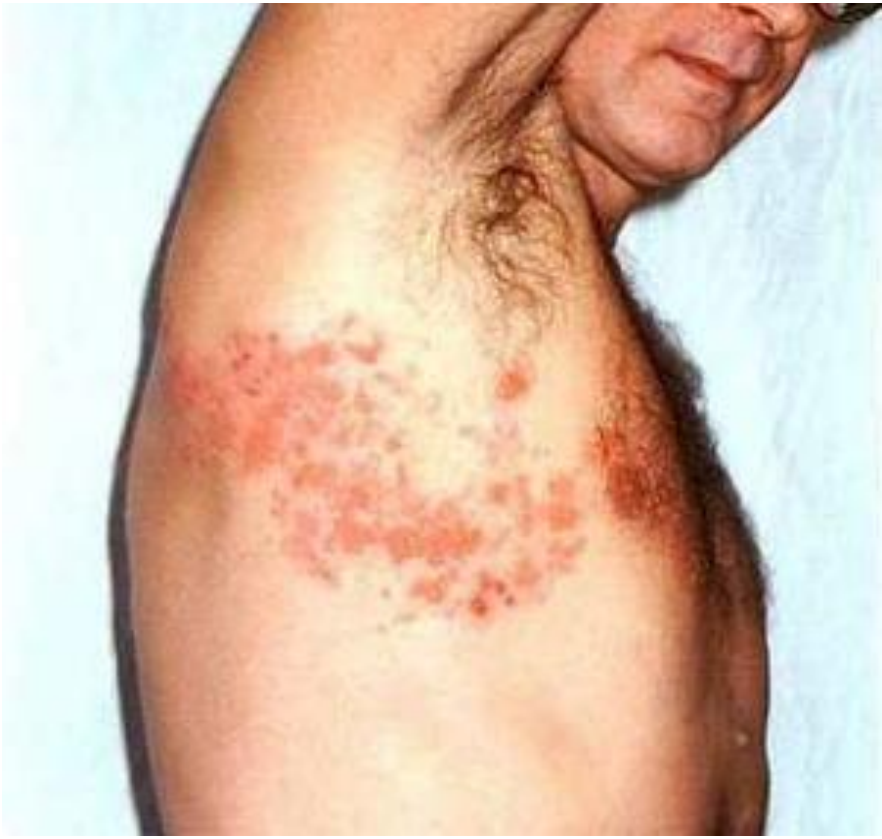


Herpes Zoster (Shingles)

- Herpes Zoster mainly affect a single dermatome of the skin.
- It may occur at any age but the vast majority of patients are more than 50 years of age.
- The latent virus reactivates in a sensory ganglion and tracks down the sensory nerve to the appropriate segment.
- There is a characteristic eruption of vesicles in the dermatome which is often accompanied by intensive pain which may last for months (postherpetic neuralgia).
- As with varicella, herpes zoster is a far greater problem in immunocompromised patients in whom the reactivation occurs earlier in life and multiple attacks occur as well as complications.

Shingles





Laboratory Diagnosis

The clinical presentations of varicella or zoster are so characteristic that laboratory confirmation is rarely required. Laboratory diagnosis is required only for atypical presentations, particularly in the immunocompromised.

- Virus Isolation - rarely carried out as it requires 2-3 weeks for a results.
- Direct detection - electron microscopy may be used for vesicle fluids but cannot distinguish between HSV and VZV. Immunofluorescense on skin scrappings can distinguish between the two.
- Serology - the presence of VZV IgG is indicative of past infection and immunity. The presence of IgM is indicative of recent primary infection.

Management

- Uncomplicated varicella is a self limited disease and requires no specific treatment. However, acyclovir had been shown to accelerate the resolution of the disease and is prescribed by some doctors.
- Acyclovir should be given promptly immunocompromised individuals with varicella infection and normal individuals with serious complications such as pneumonia and encephalitis.
- herpes zoster in a healthy individual is not normally a cause for concern. The main problem is the management of the postherpetic neuralgia.
- The International Herpes Management Forum recommends that antiviral therapy should be offered routinely to all patients over 50 years of age presenting with herpes zoster.
- Three drugs can be used for the treatment of herpes zoster: acyclovir, valicyclovir, and famciclovir. There appears to be little difference in efficacy between them.

Prevention

- Preventive measures should be considered for individuals at risk of contracting severe varicella infection e.g. leukaemic children, neonates, and pregnant women
- Where urgent protection is needed, passive immunization should be given. Zoster immunoglobulin (ZIG) is the preparation of choice but it is very expensive.
- A live attenuated vaccine is available. There had been great reluctance to use it in the past, especially in immunocompromised individuals since the vaccine virus can become latent and reactivate later on.
- However, recent data suggests that the vaccine is safe, even in children with leukaemia provided that they are in remission.
- It is highly debatable whether universal vaccination should be offered since chickenpox and shingles are normally mild diseases.

Epstein-Barr Virus

Epstein-Barr Virus (EBV)

- Belong to the gammaherpesvirus subfamily of herpesviruses
- Nucleocapsid 100 nm in diameter, with 162 capsomers
- Genome is a linear double stranded DNA molecule with 172 kbp
- The viral genome does not normally integrate into the cellular DNA but forms circular episomes which reside in the nucleus.
- EBV is able to immortalize B-lymphocytes in vitro and in vivo
- Two strains A and B. cell receptors are CR2 and CD21

Disease Association

1. Infectious Mononucleosis
2. Burkitt's lymphoma
3. Nasopharyngeal carcinoma
4. Lymphoproliferative disease and lymphoma in the immunosuppressed.
5. X-linked lymphoproliferative syndrome
6. Chronic infectious mononucleosis
7. Oral leukoplakia in AIDS patients
8. Chronic interstitial pneumonitis in AIDS patients.

Infectious Mononuclosis

- Primary EBV infection is usually subclinical in childhood. However in adolescents and adults, there is a 50% chance that the syndrome of infectious mononucleosis (IM) will develop.
- IM is usually a self-limited disease which consists of fever, lymphadenopathy and splenomegaly. In some patients jaundice may be seen which is due to hepatitis. Atypical lymphocytes are present in the blood.
- Complications occur rarely but may be serious e.g. splenic rupture, meningoencephalitis, and pharyngeal obstruction.
- Diagnosis of IM is usually made by the heterophil antibody test and/or detection of EBV IgM.
- There is no specific treatment.

Diagnosis

- Acute EBV infection is usually made by the heterophil antibody test and/or detection of anti-EBV IgM.
- Cases of Burkitt's lymphoma should be diagnosed by histology. The tumour can be stained with antibodies to lambda light chains which should reveal a monoclonal tumour of B-cell origin. In over 90% of cases, the cells express IgM at the cell surface.
- Cases of NPC should be diagnosed by histology.
- A patient with with non-specific ENT symptoms who have elevated titres of EBV IgA should be given a thorough examination.

Cytomegalovirus

Properties

- Belong to the betaherpesvirus subfamily of herpesviruses
- double stranded DNA enveloped virus
- Nucleocapsid 105nm in diameter, 162 capsomers

- Transmission may occur in utero, perinatally or postnatally. Once infected, the person carries the virus for life which may be activated from time to time, during which infectious virions appear in the urine and the saliva.
- Reactivation can also lead to vertical transmission. It is also possible for people who have experienced primary infection to be reinfected with another or the same strain of CMV, this reinfection does not differ clinically from reactivation.

Clinical Manifestations

- Congenital infection - may result in cytomegalic inclusion disease
- Perinatal infection - usually asymptomatic
- Postnatal infection - usually asymptomatic. However, in a minority of cases, the syndrome of infectious mononucleosis may develop which consists of fever, lymphadenopathy, and splenomegaly. The heterophil antibody test is negative although atypical lymphocytes may be found in the blood.
- Immunocompromised patients such as transplant recipients and AIDS patients are prone to severe CMV disease such as pneumonitis, retinitis, colitis, and encephalopathy.
- Reactivation or reinfection with CMV is usually asymptomatic except in immunocompromised patients.

Cytomegalic Inclusion Disease

- CNS abnormalities - microcephaly, mental retardation, spasticity, epilepsy, periventricular calcification.
- Eye - choroidoretinitis and optic atrophy
- Ear - sensorineural deafness
- Liver - hepatosplenomegaly and jaundice which is due to hepatitis.
- Lung - pneumonitis
- Heart - myocarditis
- Thrombocytopenic purpura, Haemolytic anaemia
- Late sequelae in individuals asymptomatic at birth - hearing defects and reduced intelligence.

Laboratory Diagnosis

- Direct detection
  - The pp65 CMV antigenaemia test is now routinely used for the rapid diagnosis of CMV infection in immunocompromised patients.
  - PCR
- Virus Isolation
  - Cell culture, requires up to 4 weeks for result.
  - DEAFF test which can provide a result in 24-48 hours.
- Serology
  - the presence of CMV IgG antibody indicates past infection.
  - The detection of IgM is indicative of primary infection although it may also be found in immunocompromised patients with reactivation.

CMV pp65 antigenaemia test

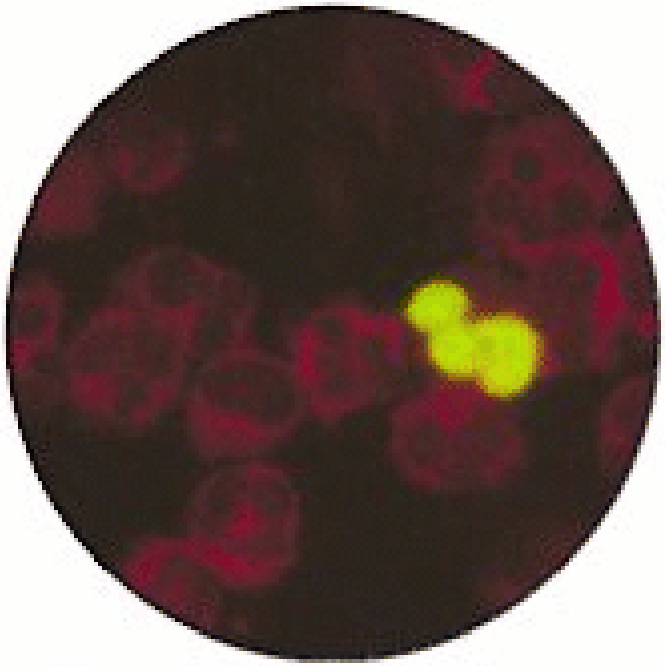


Figure 4 CMV pp65 antigens detected in nuclei of peripheral blood neutrophils

DEAFF test for CMV

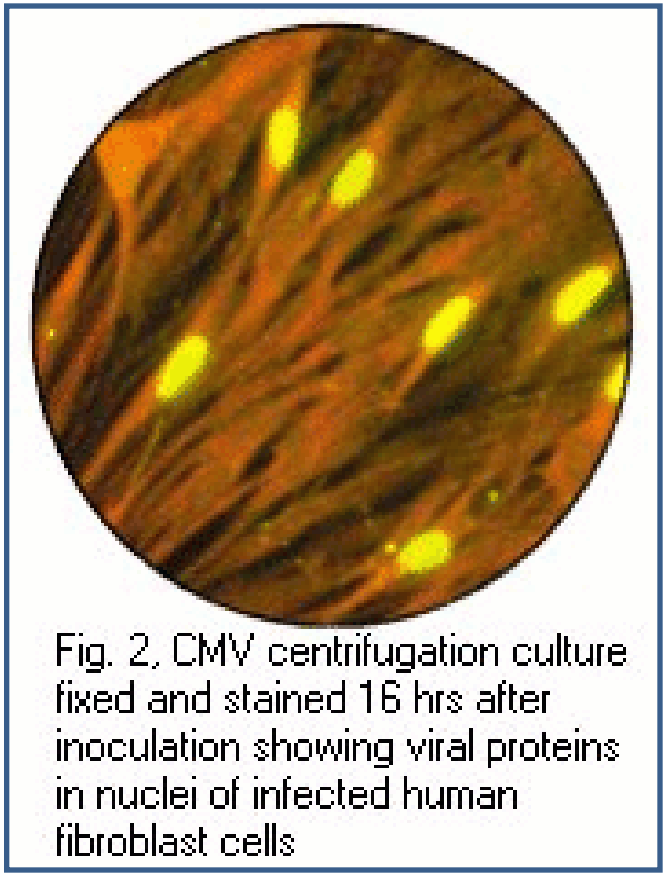


Fig. 2. CMV centrifugation culture fixed and stained 16 hrs after inoculation showing viral proteins in nuclei of infected human fibroblast cells

(Virology Laboratory, New-Yale Haven Hospital)

Treatment

- Congenital infections - it is not usually possible to detect congenital infection unless the mother has symptoms of primary infection. If so, then the mother should be told of the chances of her baby having cytomegalic inclusion disease and perhaps offered the choice of an abortion.
- Perinatal and postnatal infection - it is usually not necessary to treat such patients.
- Immunocompromised patients - it is necessary to make a diagnosis of CMV infection early and give prompt antiviral therapy. Anti-CMV agents in current use are ganciclovir, forscarnet, and cidofovir.

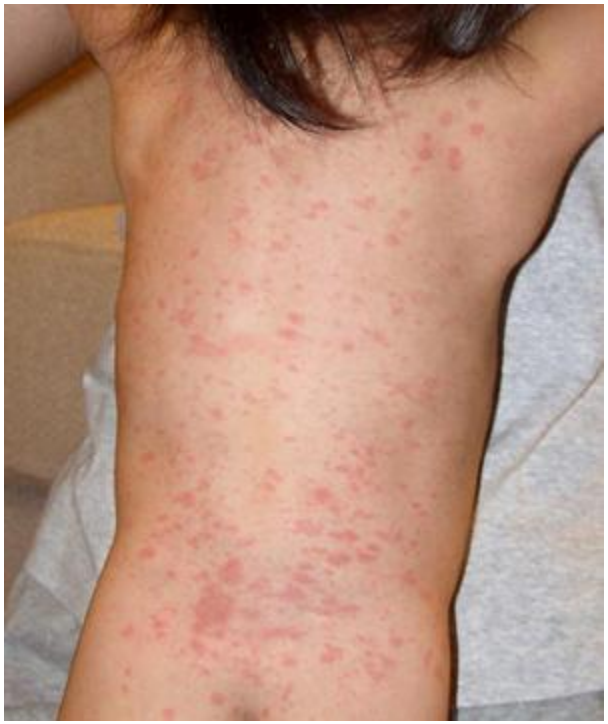
Roseola Infantum (Exanthem Subitum)

- Common in 6 months- 4 years
- Sudden rash.
- HHV6, HHV7.
- EBV, Adenovirus, coxsakieviruses and echoviruses cause similar manifestations.
- Abrupt fever, convulsions and leukopenia.
- 3-5 days later Faint macular rash appears.

- Diagnosis: seroconversion, culture and PCR

- Treatment: ganciclovir and foscarnet.

Roseola infantum



Human Herpes Virus 8

- Belong to the gammaherpesviruses subfamily of herpesviruses
- Originally isolated from cells of Kaposi's sarcoma (KS)
- Now appears to be firmly associated with Kaposi's sarcoma as well as some lesser known malignancies such as Castleman's disease and primary effusion lymphomas
- HHV-8 DNA is found in almost 100% of cases of Kaposi's sarcoma
- Most patients with KS have antibodies against HHV-8
- The seroprevalence of HHV-8 is low among the general population but is high in groups of individuals susceptible to KS, such as homosexuals.

Kaposi Sarcoma