Betaherpesvirinae

- **Cytomegalovirus (HHV5/CMV)**
- **Roseolovirus (HHV6 & 7)**

CYTOMEGALOVIRUS

- CMV is thought to be amongst the “oldest” type of herpesvirus in evolutionary terms.
- CMV is the prototype of beta-herpesviruses
- CMV found in many species, and is species specific
- CMV infection is of primary concern in immunocompromised (AIDS) and transplant patients

CYTOMEGALOVIRUS EPIDEMIOLOGY

- Humans are the only reservoir for human CMV and transmission occurs by person to person contact
- CMV is very labile and close or intimate contact is necessary for spread of infection
- Sources of infection include oropharyngeal secretions, urine, cervical and vaginal secretions, breast milk, tears, faeces and blood

CYTOMEGALOVIRUS EPIDEMIOLOGY

- Intermittant shedding of CMV from many sites is common in seropositive hosts
- Up to 60% of children become infected before 14 years. Prevalence in adults varies widely (40-100%) and is dependent on geography and socioeconomic status of the population.
- Sero-positivity approaches 100% in AIDS populations. Rate of recurrent infections with severe disease is high in this group.
- Virus excretion may last for years in congenital, perinatal and early post-natally infected hosts.

CYTOMEGALOVIRUS PATHOLOGY

- In the human CMV primarily infects ductal epithelial cells and seldom fibroblasts (predominantly in vitro). The reason for this paradox is unknown.
- Often the salivary gland becomes infected and is probably site of chronic infection.
- Viruria is a consistent feature of CMV infection in all age groups and results from renal involvement.

CYTOMEGALOVIRUS PATHOLOGY

- Infection of the liver may result in hepatitis. This is a common feature of congenital infection
- In congenital infections, sensorineural hearing loss, microcephaly and periventricular calcification may occur.
- The lungs, CNS and gatrointestinal tract may be involved particularly in immunocompromised hosts

CYTOMEGALOVIRUS PATHOGENESIS

- CMV possesses low pathogenicity. Viral replication is slow, and the virus is cell associated limiting rapid spread.
- The host's immune system is better able to contain the destructive effects of virus infection.
- Because of the large number of genetic variants that exist, it is conceivable that some strains of CMV are more virulent than others
- As CMV can clearly cause disease in various organs, it must have evolved intrinsic and extrinsic mechanisms assuring its survival and persistence in the human host
- CMV is immunosuppressive and dampens host immune responses

CYTOMEGALOVIRUS CLINICAL

Normal Host

- Primary infection in the normal host usually results in mononucleosis (about 8% of IM cases; majority by EBV)
- Rare complications include pneumonia, hepatitis and CNS disease
- Infection induces both a humoral (IgM, IgG and IgA) and CMI response.
- In children < 7 yrs CMV infection may result in severe liver, or respiratory disease
- Recurrent disease is rare in the normal host but common in the immunocompromised

CYTOMEGALOVIRUS CLINICAL

Immunocompromised Hosts

- Both morbidity and mortality is increased with primary and recurrent infections in the immunocompromised
- The immune response is the main controlling factor for maintaining the latent state in seropositive hosts
- Viral excretion is more intense and prolonged with immunosuppression, and chronic viraemia may occur.
- The antibody response is similar in primary infection and reactivation, but CMI is depressed.

CYTOMEGALOVIRUS CLINICAL

Immunocompromised Hosts

- Recurrent infections may be severe and/or fatal in transplant and AIDS patients with pneumonia and CNS disease as the most serious manifestations
- Commonly associated with allograft rejection
- Predisposes to fatal bacterial, fungal and parasitic infections
- CMV is leading cause of morbidity and mortality in immunocompromised hosts

CYTOMEGALOVIRUS CLINICAL

Congenital Infections

- **CMV is the leading viral cause of congenital abnormalities**
- **Most common cause of viral mental retardation in Western world**
- **0.2 – 2% of all infants are infected *in utero.* 10% of these will develop significant or permanent brain damage**

CYTOMEGALOVIRUS CLINICAL

Congenital Infections

Risk Factors

- **Primary CMV infection in first six months of pregnacy results in a 30- 40% risk of foetal infection**
- **Foetal infection has a 10-15% risk of causing abnormalities**
- **Recurrent CMV infection during pregnancy has a 0.5-1% risk of foetal infection and a low risk of causing abnormality**

CYTOMEGALOVIRUS CLINICAL

Perinatal Infections

- Perinatal infection is much more common 30-57%
- Can be acquired during exposure to virus in the maternal genital tract at delivery, through breast milk, saliva or by blood transfusion.
- Usually results in subclinical infections
- Excluded from congenital infection by demonstrating an absence of virus shedding at delivery.
- CMV can be the cause of pneumonia in these infants, especially when < 6 months of age.

CYTOMEGALOVIRUS DIAGNOSIS

- Methods currently used successfully for the diagnosis of CMV infections are:
  - virus isolation (fibroblasts)
  - seroconversion (IgM and IgG)
  - antigenemia - ie detection of significant proteins in cells by Mab staining (pp65)
  - polymerase chain reaction

- Best way to diagnose primary CMV infection in the normal host is by virus isolation from PBMC in fibroblasts, AND sero-conversion.

CYTOMEGALOVIRUS DIAGNOSIS

Diagnosis in the immunocompromised host by PCR and antigenemia of PBMC.

The only definitive means for diagnosing congenital CMV infection is by detection of virus during the first 3 weeks after delivery. Usually PCR and isolation from urine.

HUMAN HERPESVIRUS - 6

Roseolovirus (HHV6 & 7)

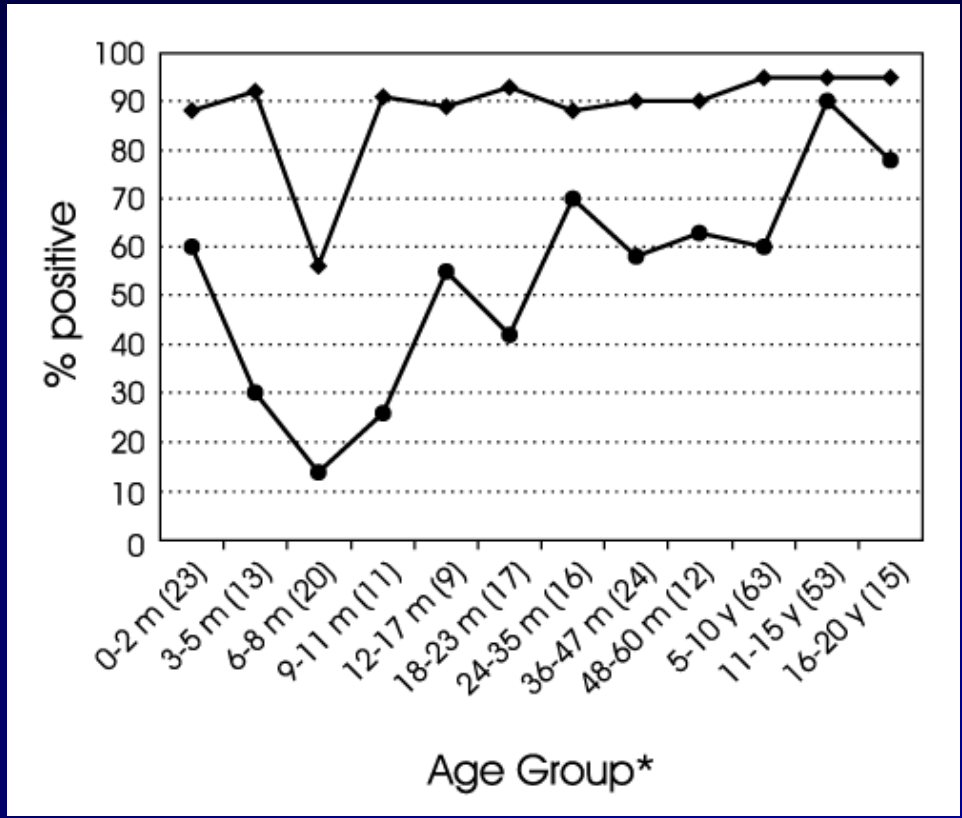
HUMAN HERPESVIRUS - 6

- First isolated from PBMC of patients in 1986 during attempts to isolate HIV
- Later isolated from patients in Africa and the UK and subsequently was found to be ubiquitous.
- Grows predominantly in activated lymphocytes – suggests gamma herpesvirus like EBV
- Genetic similarity and growth cycle to CMV led to classification as a beta-herpesvirus
- Two variants of HHV-6 have been identified on basis of genetic and biological properties (variants A and B)

HUMAN HERPESVIRUS - 6

EPIDEMIOLOGY

- HHV-6 is ubiquitous in the human population, 90-100% of healthy adults have IgG antibodies.
- Children are primarily infected between 6 months and 2 years of age. Adults rarely present with primary infection.



HUMAN HERPESVIRUS - 6

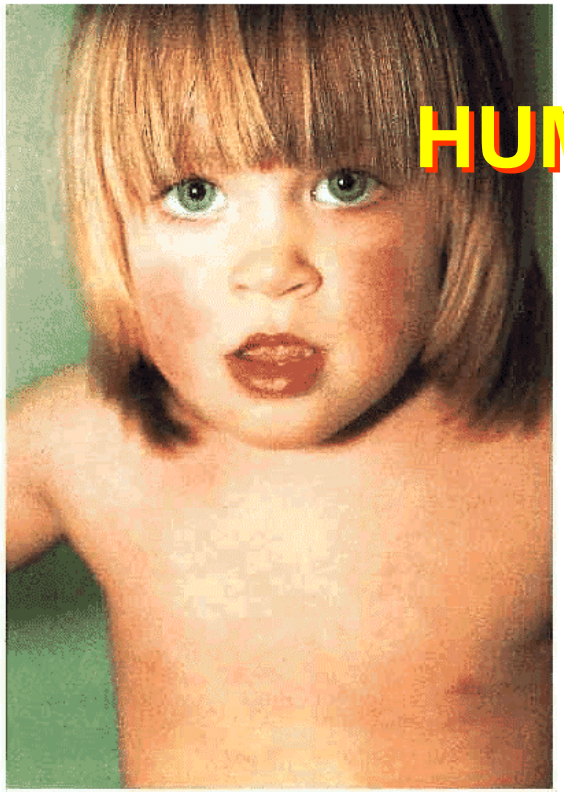
PATHOGENESIS

- HHV-6 can be readily isolated from the blood of children with primary infection but not from healthy children or adults
- Yet HHV-6 DNA can be detected in the mononuclear cells isolated from the blood of healthy adults by PCR
- Virus can be frequently isolated from the PMNC of HIV patients and transplant recipients.

HUMAN HERPESVIRUS - 6

PATHOGENESIS

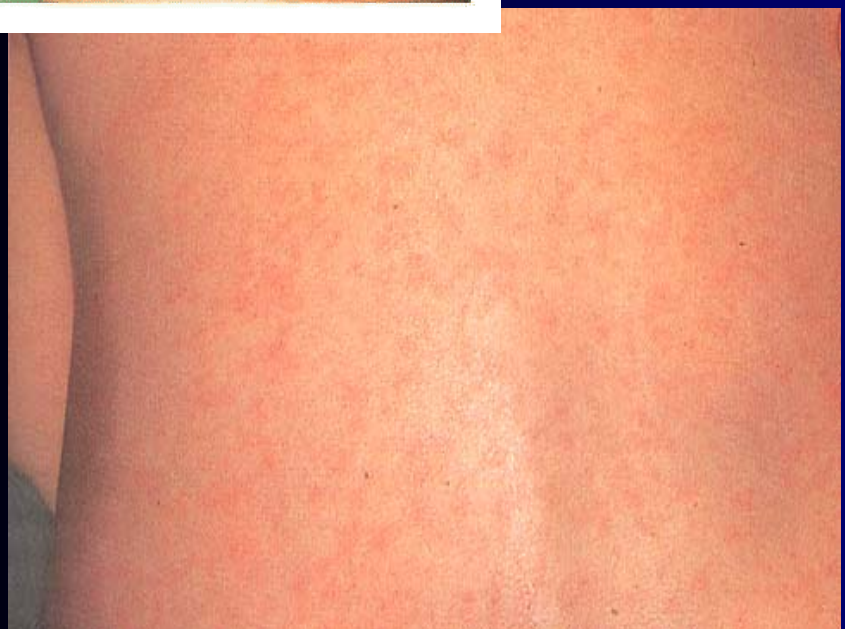
- In primary infection, IgM is detectable 5-7 days after onset of symptoms (rash) peaks at 2-3 weeks and disappears after 2 months
- Reactivation of HHV-6 infection also occurs in immuno-suppressed (suggests CMI is important). Little is known about its mechanism.
- Mechanisms for latency have not been defined as yet.
- Suggestion that HHV-6 may be a co-factor in the progression of AIDS. HHV-6 proteins can transactivate the HIV LTR



HUMAN HERPESVIRUS - 6

Primary Infection

- **HHV-6 causes exanthem subitum (Roseola) in children**
  - **Benign disease**
  - **Fever, rash**
  - **Complications include febrile convulsions**
  - **60-70% of infections are unapparent**
  - **Variant B is predominant cause**



HUMAN HERPESVIRUS - 6

Primary Infection

- Serious complications of primary infections include
  - Hepatitis, fatal fulminant hepatitis
  - Meningitis and encephalitis

- Infectious mononucleosis-like syndrome has been reported in adults and children.

HUMAN HERPESVIRUS - 6

Recurrent Infection

- The role of HHV-6 in post-transplantation disease has not been well defined.
- Reactivation has been demonstrated in renal, liver and bone marrow transplant recipients.
- Serious disease reported in BMT recipients, with interstitial pneumonia, fatal encephalitis and marrow suppression

HUMAN HERPESVIRUS - 6

Malignancy

- HHV-6 DNA may transform certain cells. However a direct link between HHV-6 and malignancy has not been proven as yet.

- Epidemiological studies suggest an association between HHV-6 and a number of tumours (HD, NHL).

HUMAN HERPESVIRUS - 6

Chronic Disease

- Evidence suggests that HHV-6 may cause various collagen vascular diseases.
- Present studies examine the role of HHV-6 in chronic fatigue syndrome.
- Recent evidence has shown HHV-6 as a possible cause of serious CNS disease such as multiple sclerosis.

HUMAN HERPESVIRUS - 6

DIAGNOSIS

- Clinically HHV-6 is often confused with other febrile syndromes involving rash. (measles, rubella, parvovirus, echovirus)
- In children the most effective diagnosis is the isolation of HHV-6 from PBMC during the symptomatic phase, together with seroconversion.
- For reactivated infections in immunocompromised adults, HHV-6 may be isolated from PBMC and detected in serum by PCR
- CNS disease may be diagnosed by the detection of HHV-6 DNA in the CSF

HUMAN HERPESVIRUS - 7

- HHV-7 was first isolated from a healthy adult in 1992
- Frequently isolated from the saliva of most healthy adults.
- Shown to be distinct from other herpesviruses incl. HHV-6
- Both viruses have common proteins, but also unique proteins

HUMAN HERPESVIRUS - 7

BIOLOGICAL PROPERTIES

- HHV-7 appears to act as a helper virus for HHV-6 reactivation in vitro.
- Sero-prevalence studies show infection with HHV-7 occurs later than HHV-6
- 80-85% of healthy adults have antibodies to HHV-7
- There is no clear evidence for the involvement of HHV-7 in human disease. HHV-7 has been isolated from a patient with Roseola