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
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**

- Intermittent 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.
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.
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 gastrointestinal tract may be involved particularly in immunocompromised hosts.
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.
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
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
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
Congenital Infections

Risk Factors

• Primary CMV infection in first six months of pregnancy 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
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)
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.
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
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).
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
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.