

Cytomegalovirus, Epstein-barr Virus, HHV-6, AND HHV- 7

Janet Wong, M.D.

Cytomegalovirus

- Herpesviridae
- 200 nm in diameter
- Double stranded DNA icosahedral capsid
- Lipid-containing envelope (acquired from host cell nuclear membrane or cytoplasmic vacuoles)
- Fusion: envelope glycoproteins and cell surface proteins

Cytomegalovirus Epidemiology

- Present in all areas of world
- No seasonal variation
- No non-human vectors (human CMV)
- Acquisition occurs at an earlier age in underdeveloped countries
- Day-care and increased breast feeding has increased infection in younger children in developed countries
- Most common cause of congenital infection in the United States

Cytomegalovirus Transmission

- Direct or indirect person-to-person contact
- Requires close or intimate contact with infected secretions:
 - urine - oropharyngeal secretions
 - semen - vaginal secretions
 - tears - breast milk
 - blood - transplanted organs
- Virus excretion persists for years
 - congenital
 - peripartum
 - postnatal
- CMV may persist on fomites for hours
 - ingestion
 - sexual
 - transplacental

Cytomegalovirus Perinatal Transmission

- Intrauterine: 0.2-2.2% (only 5% symptomatic)
- Maternal primary infection: 30-40%
- Maternal recurrent infection: 0.9-1.5%
- Intrapartum: 2.5%
- CMV detected in genital tract: 30-40%
- Breast feeding: 5-15%
 - CMV positive mother with >1 month of breast feeding: 30-70%

Cytomegalovirus Clinical Syndromes

- Asymptomatic
- Congenital infection
- Neonatal infection in premature infants
- Mononucleosis syndrome
- Immunosuppressed patients
 - Interstitial pneumonitis
 - Retinitis • Colitis
 - Hepatitis • Meningoencephalitis

Cytomegalovirus Congenital infection

- Intrauterine transmission
- Maternal immunity (prior infection) affords protection (humoral ± cellular)
- Effect of gestational age (primary infection)
 - no effect on rate of transmission
 - the earlier in gestation, the greater chance for severe sequela
- Organs involved
 - CNS - encephalitis; microcephaly
 - sensorineural deafness
 - Liver - hepatitis
 - Hematopoietic
 - anemia
 - thrombocytopenia
 - extramedullary hematopoieses
 - Eye
 - chorioretinitis
 - optic neuritis
 - Lung
 - pneumonitis
 - Teeth
 - defect in enamel
 - Spleen
 - splenomegaly

Cytomegalovirus

Congenital infection: Long-term sequelae

	Maternal Primary	Maternal Recurrent
Any hearing loss	15%	5%
Bilateral hearing loss	8%	0
Chorioretinitis	6%	2%
IQ <70	13%	0
Seizures	5%	0

	Symptomatic	Asymptomatic
Any hearing loss	58%	7.4%
Bilateral hearing loss	37%	2.7%
Chorioretinitis	20%	2.5%
IQ <70	55%	3.7%
Seizures	23%	1%

Cytomegalovirus Diagnosis

- Detection of CMV
 - Tissue culture
 - Shell viral assay
 - Antigen detection
 - Viral DNA detection
 - qualitative PCR
 - quantitative PCR
 - in situ hybridization
 - Histology
- Serology
 - CMV IgG
 - CMV IgM (high rate of false positives and false negatives)
- Intrauterine infection -- detection of virus in first 2 weeks of life
- Natal infection -- negative cultures in first 2 weeks of life with positive culture from 3 to 12 weeks of age
- Postnatal infection:
 - seroconversion optimal for timing
 - presence of virus documents infection not timing
 - quantitative PCR may be predictive of risk for disease or presence of disease in immunocompromised

Cytomegalovirus Treatment

- Available agents
 - ganciclovir
 - foscarnet
 - cidofovir
 - CMV hyperimmune globulin
- Indications
 - life threatening infections in immunocompromised patients
 - ? symptomatic congenital infection

Cytomegalovirus Prevention

- Hyperimmune globulin
- Vaccines (still in development)
- Condoms
- Good hygiene, especially Handwashing in hospital, day care centers
- Donor screening of blood/organ donors
- Reducing viable leukocytes in blood product (eg, filtering; frozen-deglycerolized)

Epstein-barr Virus

- 120 nm in diameter
- Double stranded DNA
- Icosahedral capsid
- Lipid-containing envelop
- Infects human and primate B lymphocytes
- Cells latently infected with EBV grow continuously
- Present in all parts of the world
- No seasonal variation
- Acquisition occurs at an earlier age in underdeveloped countries
 - adolescent seroprevalence:
 - undeveloped: >90%
 - developed: 40-50%

Epstein-Barr Virus Pathogenesis

- Infection of B cells
- Up to 20% are infected
- Mono- and poly-clonal proliferation
- Immortalization of B cells
- Atypical lymphocytes - cytotoxic suppressor T lymphocytes
 - outnumber B cells 50 to 1
 - kill infected B cells

Epstein-Barr Virus Transmission

- Excreted in oropharyngeal secretions (low titer of virus even during acute illness)
- Blood products

Epstein-barr Virus Clinical Manifestations

- Asymptomatic (frequency inversely related to age)
- Mononucleosis syndrome
- Burkitt lymphoma
- Nasopharyngeal carcinoma

Epstein-Barr Virus Clinical Manifestations

- Syndromes in immunocompromised hosts
 - x-linked lymphoproliferative syndrome
 - post-transplant B cell lymphoproliferative disorders
 - HIV-associated B cell lymphoma
 - HIV - associated oral “hairy” leukoplakia
 - HIV-associated lymphocytic interstitial pneumonitis
 - HIV-associated leiomyosarcoma

Epstein-Barr Virus Mononucleosis Syndrome

- Fever
- Lymphadenopathy
- Pharyngitis
- Splenomegaly
- Hepatitis
- Skin rash (illness and drug-associated)
- Pneumonitis
- CNS
- Myocarditis
- Thrombocytopenia
- Anemia
- Granulocytopenia

Epstein-Barr Virus X-linked Lymphoproliferative

Syndrome

- Lymphoproliferative response 75%
 - fatal mononucleosis
 - lymphoma (usually Burkitt-type)
 - hemophagocytic syndrome
- Aroliferative response 25%
 - hypogammaglobulinemia
 - aplastic anemia
 - agranulocytosis
 - recurrent bacterial infections
 - late malignancies

Epstein-Barr Virus Diagnosis

- Clinical syndrome
- Hematologic abnormalities
- Heterophile antibodies
- Antibodies to EBV antigens
- Histology
 - virus genome (PCR and DNA hybridization)
 - virus antigens (EBNA)

Epstein-Barr Virus Heterophile Antibodies

- Cause agglutination of sheep red blood cells after absorption with guinea pig kidney antigens but not after absorption with beef red blood cells
- Antibodies of IgM class
- Rapid test uses equine or bovine erythrocytes
- Frequency of positive heterophile Ab in IM increases
 - with age (rare with age <5 years)
 - with time after onset of symptoms

Epstein-Barr Virus Diagnosis

	<u>VCA-IgM</u>	<u>VCA-IgG</u>	<u>EBNA</u>
No prior infection	-	-	-
Primary infection	+	+++	-
Convalescent/post infection	-	++	+

Epstein-barr Virus: Treatment

- Supportive care
- Corticosteroids for life-threatening manifestations
- Avoid contact sports until spleen not palpable
- Antiviral therapy: acyclovir or ganciclovir
 - activity on lytic phase of EBV
 - no activity on latent phase of EBV
 - not indicated for mononucleosis
 - may have role in immunocompromised patients

Human Herpesvirus 6

- Herpesviridae
- Double stranded DNA, icosahedral capsid
- Preferentially infects native T lymphocytes, especially activated CD4 + cells
- May also infect other T cells, B cells, natural killer cells, astrocytes and macrophages. Macrophage may be site of latency
- Two types: A and B
 - A - isolated from adults, no disease yet
 - B - roseola and other febrile illnesses
- Worldwide
- No seasonal predilection
- Primary infection common in first year of life; peak in second 6 months of life
- Major cause of febrile illness in infants 6-18 months of age; 20% of ER visits for this age group

Human Herpesvirus 6 Transmission

- Not completely elucidated
- Possibly acquired from asymptomatic shedding in secretions of family members
- Virus present in serum and respiratory secretions of infants with roseola
- Virus present in saliva and salivary glands of healthy adults
- Transplacental transmission - possible
- Breast milk - not likely

Human Herpesvirus 6 Clinical Manifestations

- High Fever (frequently with no localizing signs)
- Irritability
- Adenopathy (cervical and occipital)
- Maculopapular rash (25%; during < after fever)
- Inflamed tympanic membranes
- URI symptoms: coryza; pharyngitis
- GI symptoms: vomiting and diarrhea
- Bulging anterior fontanelle
- Febrile seizures (15%)
- Less Common Manifestations
 - arthritis
 - hepatitis
 - heterophile - negative mononucleosis
 - meningoencephalitis
 - thrombocytopenia
 - sinus histiocytosis with massive lymphadenopathy
 - syndromes in immunocompromised patients
 - suppression of marrow in bone marrow transplant
 - interstitial pneumonitis in bone marrow transplant

Human Herpesvirus 6 Diagnosis

- Clinical syndrome
- Hematologic: relative neutropenia and lymphopenia
- Tissue culture of peripheral blood lymphopenia rare except during primary infection)
- Serology
 - numerous IgG assays
 - IgM response not reliable
- PCR (positive in acute and past infection)

Human Herpesvirus 6 Therapy

- Supportive care, especially control of fever
- HHV-6 susceptible to ganciclovir and foscarnet in vitro

Human Herpesvirus 7

- Herpesviridae
- Double stranded DNA, icosahedral capsid
- Infects predominately CD4 + cells; does not infect B cells, macrophages or thymocytes

Human Herpesvirus 7 Epidemiology

- Frequent infections of childhood
- Occurs later than HHV-6
- HHV-7 seroprevalence
 - 1 year --20%
 - 2 years -- 40%
 - 3 years -- 50%
 - adults - 80-90%
- Acquisition of HHV-7 is independent of HHV-6

Human Herpesvirus 7 Transmission

- Not completely elucidated
- Isolated from saliva and peripheral blood lymphocytes
- 75% of adults have HHV-7 in their saliva

Human Herpesvirus 7 Clinical Manifestations

- Fever
- Maculopapular rash
- Irritability
- Lymphadenopathy
- Mild diarrhea

Human Herpesvirus 7 Diagnosis

- Clinical syndrome
- Tissue culture isolation
- Serology
- PCR

Kaposi Sarcoma-Associated Herpes Virus (Human Herpesvirus 8)

- Kaposi's sarcoma
- Monoclonal B cell lymphomas in HIV (malignant effusion type rather than adenopathy)