Lec.3 Herpesviruses

Date:10/4/2025

The herpesviruses that commonly infect humans include herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicellazoster virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpesviruses 6 and 7, and herpesvirus 8 (Kaposi sarcoma-associated herpesvirus [KSHV]). Herpes B virus of monkeys can also infect humans.

PROPERTIES OF HERPESVIRUSES

Important properties of herpesviruses include:

Virion: Spherical, 150–200 nm in diameter (icosahedral)
Genome : Double-stranded DNA, linear, 125–240 kbp.
Proteins: More than 35 proteins in virion
Envelope: Contains viral glycoproteins, Fc receptors
Replication: Nucleus, bud from nuclear membrane

Outstanding characteristics:
Encode many enzymes; Establish latent infection; Persist indefinitely in infected hosts Frequently reactivated in immunosuppressed hosts; Some cause cancer.

HERPES SIMPLEX VIRUSES

HSV-1 and **HSV-2** infect epithelial cells and establish latent infections in neurons. Type 1 is classically associated with oropharyngeal lesions and causes recurrent attacks of "fever blisters." Type 2 primarily infects the genital mucosa and is mainly responsible for genital herpes. Both viruses also cause neurologic disease. HSV-1 is the leading cause of sporadic encephalitis. Both types 1 and 2 can cause neonatal infections that are often severe.

Pathogenesis and Pathology

HSV is transmitted by contact of a susceptible person with an individual excreting virus. The virus must encounter mucosal surfaces or broken skin for an infection to be initiated (unbroken skin is resistant).
Herpes simplex virus type 1 is usually associated with oropharyngeal lesions, and type 2 primary cause genital infections. HSV1 and HSV2 establish latency in nerve cells.
Viremia is more common during primary HSV-2 infections than during HSV-1 infections. Lestion are due to necrosis of infected cells together with the inflammatory response. Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble those of varicella-zoster virus.

Clinical finding

Oropharyngeal disease, keratoconjunctivitis and genital herpes. Genital disease is usually caused by HSV-2, although HSV-1 can also cause clinical episodes of genital herpes.

Skin Infections

These lesions are seen on the fingers of dentists and hospital personnel (herpetic whitlow) and on the bodies of wrestlers.

E. Encephalitis

Most common with HSV-1.

Neonatal herpes can be acquired postnatally by exposure to either HSV-1 or HSV-2. HSV infection of the newborn may be acquired in utero, during birth, or after birth. The mother is the most common source of infection in all cases.

Sources of infection postnatally can be acquired from family members and hospital personnel who are shedding virus.

Immunocompromised hosts are at increased risk for HSV infections.

Immunity

During primary infections IgM antibodies appear and are followed by IgG and IgA antibodies that persist for long periods.

Cell-mediated immunity and nonspecific host factors (natural killer cells, interferon) are important in controlling both primary and recurrent HSV infections.

Laboratory Diagnosis

Methods include: 1. Polymerase Chain Reaction (PCR), 2. Isolation and Identification of Virus, 3. Cytopathology, 4. Serology.

Epidemiology

HSV are worldwide in distribution. No animal reservoirs or vectors are involved with the human viruses. Transmission is by contact with infected secretions. The epidemiology of HSV-1 and HSV-2 differs. The highest incidence of HSV-1 infection occurs among children 6 months to 3 years of age. By adulthood, 70–90% of persons have type 1 antibodies. There is a high rate of geographic variation in seroprevalence. HSV-2 is usually acquired as a sexually transmitted disease, so antibodies to this virus are seldom found before puberty.

Treatment

Several antiviral drugs have proved effective against HSV infections, including acyclovir, valacyclovir, and vidarabine.

VARICELLA-ZOSTER VIRUS

Varicella (chickenpox) is a mild, highly contagious disease, chiefly of children, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. The disease may be severe in adults and in immunocompromised individuals. Zoster (shingles) is a sporadic, disease of elderly or immunocompromised individuals that is characterized by pain and a rash limited in distribution to the skin innervated by a single sensory ganglion. The lesions are similar to those of varicella.

Pathogenesis and Pathology

A. Varicella

The route of infection is the mucosa of the upper respiratory tract or the conjunctiva. The pathogenesis of primary infection with varicella-zoster virus include incubation period lasts from 10 to 21 days. Secondary viremia results in the transport of virus to skin and respiratory mucosal sites, where replication in epidermal cells causes the characteristic rash (chickenpox). Varicella-zoster virus-specific immunity is required to terminate viral replication. The virus gains access to cells of the trigeminal and dorsal root ganglia during primary infection and establishes latency.

B. Zoster Zoster usually occurs in persons immunocompromised as a result of disease, therapy, or aging, but it occasionally develops in healthy young adults, as a result of reactivation of latent VZV infection in ganglia. It usually starts with severe pain in the area of skin or mucosa supplied by one or more groups of sensory nerves and ganglia. Varicella zoster central nervous system disease, most frequently meningitis, often presents without a typical zoster rash.

Clinical Findings

A. Varicella

Subclinical varicella is unusual. The incubation period of typical disease is 10–21 days. Malaise and fever are the earliest symptoms, soon followed by the rash, first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa in the mouth. Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time. The rash lasts about 5 days, and most children develop several hundred skin lesions.

Immunity

VZV induce antibody. The development of varicella-zoster virus-specific cell mediated immunity is important in recovery from both varicella and zoster. Appearance of local interferon may also contribute to recovery.

Laboratory Diagnosis

PCR, for DNA can be detected in saliva in many patients, including those with zoster without rash, vesicle fluid, skin scrapings, and biopsy material.

Cytopathic effect: in stained smears of scrapings or swabs of the base of vesicles, multinucleated giant cells are seen.

Intracellular viral antigens can be demonstrated by immunofluorescence staining of similar smears. A rise in specific antibody titer can be detected in the patient's serum by fluorescent antibody and enzyme immunoassay.

Epidemiology

Varicella and zoster occur worldwide. Varicella spread readily by airborne droplets or by direct contact. Varicella patients is probably infectious. Varicella (chickenpox) is highly communicable and is a common epidemic disease of childhood (most cases occur in children younger than 10 years of age). Adult cases do occur. It is much more common in winter and spring than in summer in temperate climates. Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. About 10–20% of adults will experience at least one zoster attack during their lifetime, usually after the age of 50 years. Zoster patients can be source of varicella for children because viral DNA present in their saliva.

Treatment

Several antiviral compounds provide effective therapy for varicella, including acyclovir, valacyclovir, famciclovir and foscarnet.

CYTOMEGALOVIRUS

CMVs are ubiquitous herpesviruses that are common causes of human disease. CMVs are the agents of the most common congenital infection. Abortion for women, Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the CMVs. The name for the classic cytomegalic inclusion disease derives from the propensity for massive enlargement of CMV-infected cells.

Human CMV replicate *in vitro* only in human fibroblast, although the virus isolated from epithelial cells of the host.

Pathogenesis and Pathology

A. Normal Hosts

CMV may be transmitted from person to person in several different ways (Breast milk: immune complexes ; Toddlers: urine, saliva; Sex: semen, cervical secretions), all requiring close contact with virus-bearing material. The virus causes a systemic infection; it has been isolated from lung, liver, esophagus, colon, kidneys, monocytes, and T and B lymphocytes. The disease is an infectious mononucleosis-like syndrome, although most CMV infections are subclinical. CMV establishes lifelong latent infections. Virus can be shed intermittently from the pharynx and in the urine for months to years after primary infection. Salivary gland involvement is common and is probably chronic.

B. Immunosuppressed Hosts

Primary CMV infections in immunosuppressed hosts are much more severe than in normal hosts.

C. Congenital and Perinatal Infections

Cytomegalic inclusion disease. A high percentage of babies with this disease will exhibit developmental defects and mental retardation. The virus can be transmitted in utero.

Immunity

CMV induce antibodies to CMV however, reactivation of latent infection occurs in the presence of humoral immunity. The presence of antibody in breast milk does not prevent transmission of infection to breastfeeding infants. Maternal antibody protects more against development of serious disease in the infant than viral transmission.

Laboratory Diagnosis

A. Polymerase Chain Reaction (PCR) and antigen detection assays

B. Isolation of Virus

C. Serology

Many types of assays can detect CMV IgG antibodies, indicative of past infection (and the potential to undergo reactivation). Detection of viral IgM antibodies suggests a current infection.

Epidemiology

CMV is endemic in all parts of the world; epidemics are unknown. It is present throughout the year, with no seasonal variation seen in infection rates.

Treatment and Control

Treatment by Ganciclovir and Ganciclovir.

EPSTEIN-BARR VIRUS

EBV is a ubiquitous herpesvirus that is the causative agent of acute infectious mononucleosis and is associated with nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin and non-Hodgkin lymphomas, other lymphoproliferative disorders in immunodeficient individuals, and gastric carcinoma.

Pathogenesis and Pathology

A. Primary Infection

EBV is commonly transmitted by infected saliva and initiates infection in the oropharynx. Viral replication occurs in epithelial cells (or surface B lymphocytes) of the pharynx and salivary glands. Primary infections in children are usually subclinical, but if they occur in young adults, acute infectious mononucleosis often develops. Mononucleosis is a polyclonal stimulation of lymphocytes. EBV-infected B cells synthesize immunoglobulin. Autoantibodies are typical of the disease.

B. Reactivation from Latency

Reactivations of EBV latent infections can occur, as evidenced by increased levels of virus in saliva and of DNA in blood cells. These are usually clinically silent. Immunosuppression is known to reactivate infection.

Clinical Findings

Infectious mononucleosis and cancer.

Immunity

EBV infections elicit antibodies against virus, a number of cell-mediated responses, and secretion of lymphokines. Cell-mediated immunity and cytotoxic T cells are important in limiting primary infections and controlling chronic infection.

Laboratory Diagnosis

A. Molecular Assays for Identification of Virus, B. Isolation of Virus, C. Serology (ELISA).

Epidemiology

EBV is common in all parts of the world, with more than 90% of adults being seropositive. It is transmitted primarily by contact with oropharyngeal secretions 90% of children are infected by age 6 years.

Prevention, Treatment, and Control

There is no EBV vaccine available. Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration, but it does not affect the number of EBV-immortalized B cells.

HUMAN HERPESVIRUS 6

The T-lymphotropic HHV-6 was first recognized in 1986. Initial isolations were made from cultures of peripheral blood mononuclear cells from patients with lymphoproliferative disorders. The virus grows well in CD4 T lymphocytes. Other cell types also support viral replication, including B cells and cells of glial, fibroblastoid, and megakaryocyte origin. Cells in the oropharynx must become infected because virus is present in saliva.

Epidemiology and Clinical Findings

Seroepidemiologic studies using immunofluorescence tests for serum antibodies or PCR assays for viral DNA in saliva or blood cells Infections with HHV-6 typically occur in early childhood. This primary infection causes exanthem subitum (roseola infantum, or "sixth disease",) the mild common childhood disease characterized by a high fever and skin rash. The mode of transmission of HHV-6 is presumed to be via oral secretions. The fact that it is a ubiquitous agent suggests that it must be shed into the environment from an infected carrier. Infections persist for life. Reactivation appears to be common in transplant patients and during pregnancy.

HUMAN HERPESVIRUS 7

A T-lymphotropic human herpesvirus, designated HHV-7, was first isolated in 1990 from activated T cells recovered from peripheral blood lymphocytes of a healthy individual. HHV-7 is immunologically distinct from HHV-6, although they share about 50% homology at the DNA level. HHV-7 appears to be a ubiquitous agent, with most infections occurring in childhood but later than the very early age of infection noted with HHV-6. Persistent infections are established in salivary glands, and the virus can be isolated from saliva of most individuals. In a longitudinal study of healthy adults, 75% of subjects excreted infectious virus in saliva one or more times during a 6-month observation period. Similar to HHV-6, primary infection with HHV-7 has been linked with roseola infantum in infants and young children.

HUMAN HERPESVIRUS 8

Also called KSHV is the cause of Kaposi sarcomas, vascular tumors. Contact with oral secretions is likely the most common route of transmission. The virus can also be transmitted sexually, vertically, by blood, and through organ transplants. Viral DNA has also been detected in breast milk samples.

Viral DNA can be detected in patient specimens using PCR assays. Direct virus culture is difficult and impractical. Serologic assays are available to measure persistent antibody to KSHV using indirect immunofluorescence, Western blot, and enzyme-linked immunosorbent assay formats.

Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV replication

B VIRUS

Herpes B virus of Old World monkeys is highly pathogenic for humans. Transmissibility of virus to humans is limited, but infections that do occur are associated with a high mortality rate (~60%). B virus disease of humans is an acute ascending myelitis and encephalomyelitis.

Pathogenesis and Pathology

B virus infections seldom cause disease in rhesus monkeys. Vesicular lesions of the oropharynx may occur and resemble those induced in humans by HSV. Genital lesions also occur. Many rhesus monkeys carry latent B virus infections that may be reactivated by conditions of stress. The virus is transmissible to other monkeys, rabbits, guinea pigs, rats, and mice. Rabbits routinely develop fatal infections after B virus inoculation. B virus infections in humans usually result from a monkey bite, although infection by the respiratory route or ocular splash exposure is possible. The striking feature of B virus infections in humans is the very strong propensity to cause neurologic disease. Many survivors are left with neurologic impairment.

Epidemiology and Clinical Findings

B virus is transmitted by direct contact with virus or virus containing material. Transmission occurs among *Macaca* monkeys, between monkeys and humans, and rarely from human to human. Virus may be present in saliva, conjunctival and vesicular fluids, genital areas, and feces of monkeys. Respiratory transmission can occur. Other sources of infection include direct contact with animal cages and with infected monkey cell cultures.

Treatment and Control

There is no specific treatment after the clinical disease is manifest. However, treatment with acyclovir is recommended immediately after exposure.

Reference

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