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HERPES VIRAL INFECTIONS IN CHILDREN

Manual for practical lessons
for the V–VI year students

ГЕРПЕСВИРУСНАЯ ИНФЕКЦИЯ У ДІТЕЙ

Методичні вказівки до практичних занять
для студентів V–VI курсів

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INTRODUCTION

Herpes viruses are a leading cause of human viral disease, second only to influenza and cold viruses. They are capable of causing overt disease or remaining silent for many years only to be reactivated, for example as shingles. The name herpes comes from the Latin *herpes* which, in turn, comes from the Greek word *herpein* which means to creep. This reflects the creeping or spreading nature of the skin lesions caused by many herpes virus types.

There are at least 25 viruses in the family Herpesviridae (currently divided into three sub-families). Eight or more herpes virus types are known to infect man frequently.

Once a patient has become infected by herpes virus, the infection remains for life. The initial infection may be followed by latency with subsequent reactivation. Herpes viruses infect most of the human population and persons living past middle age usually have antibodies to most of the above herpes viruses with the exception of HHV-8.

ETIOLOGY AND EPIDEMIOLOGY

Herpes viruses are classified by their location in the latent state (table)

Properties of Herpes viruses					
Type	Name	Sub Family	Target cell type	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Alpha-herpesvirinae	Muco-epithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Alpha-herpesvirinae	Muco-epithelia	Neuron	Close contact usually sexual
3	Varicella Zoster virus (VSV)	Alpha-herpesvirinae	Muco-epithelia	Neuron	Contact or respiratory route
4	Epstein-Barr Virus (EBV)	Gamma-herpesvirinae	B lympho-cyte, epithelia	B lympho-cytes	Saliva
5	Cytomegalovirus (CMV)	Beta-herpesvirinae	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes and possibly others	Contact, blood transfusions, transplantation, congenital
6	Herpes lymphotropic virus	Beta-herpesvirinae	T lympho-cytes and others	T lympho-cytes and others	Contact, respiratory route
7	Human herpes virus-7 (HHV-7)	Beta-herpesvirinae	T lympho-cytes and others	T lympho-cytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma- associated herpes virus (KSHV)	Gamma-herpesvirinae	Endothelial cells	Unknown	Exchange of body fluids?

Envelope Herpes viruses are enveloped viruses. They bud from the inner nuclear membrane which has been modified by the insertion of herpes glycoproteins (in the mature virus, these glycoproteins determine the cell to be

infected because of the availability of the appropriate receptors). The viral membrane is quite fragile and a virus with a damaged envelope is not infectious (This means that the virus readily falls apart and so the virus can only be obtained by direct contact with mucosal surfaces or secretions of an infected person – it cannot be caught from toilet seats). Besides drying, the virus is also sensitive to acids, detergents and organic solvents as might be expected for an virus with a lipid envelope.

Tegument The space between the envelope and the capsid is the tegument. This contains virally-encoded proteins and enzymes involved in the initiation of replication.

Capsid These viruses have a doughnut shaped capsomere of about 100–200 nm in diameter with an icosahedral nucleocapsid. The latter contains 162 capsomeres.

Genome These viruses have double stranded DNA. The size of the genomes differs with cytomegalovirus having the largest genome.

Herpes virus replication

1) Binding to the cell surface: As with many other viruses, cell tropism is determined by the availability of the correct receptor on the surface of the cell to be infected. The virus fuses with the cell membrane at ambient pH and so there is the possibility of syncytia formation between infected cells and therefore cell to cell transmission even in the presence of neutralizing humoral antibodies. This means that cell-mediated immunity is important in suppressing herpes virus infections.

2) Nucleocapsid enters cytoplasm: The tegument-surrounded nucleocapsid is carried to the nuclear membrane where the nucleocapsid binds. The DNA genome then enters the nucleus.

3) Transcription: This is a very complex process, as might be expected from the large size of genome. There are three classes of proteins that need to be made for the production of a mature virus.

Alpha proteins: These are the immediate-early proteins. They are involved in transcriptional regulation and are not found in the mature virion. They are also involved in the control of beta protein synthesis.

Beta proteins: These are the early proteins and are involved also in DNA replication (they include the DNA polymerase and transcription factors). Only a few copies of DNA polymerase need to be made for replication to occur.

Gamma proteins: These are the late proteins and are structural components of the virus. The synthesis of gamma proteins is initiated after the start of DNA synthesis.

4) RNA transcription: The herpes DNA is transcribed to RNA by a cellular enzyme (DNA-dependent RNA polymerase I). However, the transcription of the various genes is dependent on both nuclear factors of the cell AND proteins encoded by the virus. This control of viral mRNA, and therefore, viral protein, synthesis determines whether infection will result in the production of new virus particles and cell death (a lytic infection), persistent shedding of virus (persistent infection) or latency. Whether latency occurs is the property of the host cell, that is some cells do not allow the replication of viral DNA. If the cell permits progression beyond the immediate early genes, a lytic infection will ensue.

5) DNA synthesis: Herpes viruses encode their own DNA-dependent DNA polymerase. In addition, some herpes viruses encode enzymes (such as thymidine kinase) that allow the virus to grow in non-dividing cells that do not therefore contain the precursors of DNA synthesis. Without this enzyme, neurotropic herpes viruses could not replicate because of the low amounts of certain DNA precursors in nerve cells.

6) Assembly: Nucleocapsids are assembled in the nucleus and are filled with DNA They then bud through the double nuclear membrane and leave the cell via the exocytosis pathway or they may bud through another cell membrane such as the plasma membrane.

Alphaherpesviruses are characterised by a relatively shorter replication cycle (not longer than 16–18 hrs according to the various susceptible cells); they spread well from cell to cell but they also are easily released from infected cells, in which they multiply causing clear-cut cythopatic effect and formation of eosinophilic intranuclear inclusion bodies (of type B according to Cowdry). In vitro they infect cells originating from various animal species. In nature, various species (not only humans) host many Alphaherpesviruses, but for each virus a species can be identified to which it had been at best adopted. In such host species the particular virus undergoes latency most frequently showing in it the lowest degree of pathogenicity. Within the host body, the Alphaherpesviruses prefer to spread along nerves, while intraaxonal transmission predominates.

Betaherpesviruses have a limited range of host organisms. This property is reflected in vitro when these viruses replicated only in cells derived from the host species. Their replication cycle is slow (lasts several days) and their release from infected cells is inefficient. Also betaherpesviruses develop latency. Because they do not show preferential neural spread, they usually persist in leukocytes, in cells of reticuloendothelial system and also in epithelium cells of renal tubuli and salivary gland ducts. At productive replication, infected cells become enlarged and contain intranuclear inclusion bodies.

The **Gammaherpesviruses** replicate slowly and reveal lymphotropic properties. They code for lymphokines and or other proteins influencing intracelullar signalisation. Therefore, these viruses may be related to several malignant diseases.

Pathogenesis of HSV-1 and HSV-2 Infections

The site of the initial infection is usually the oral or genital mucosa, depending on the way in which the person acquires the virus. It is often noted that HSV-1 infects above the waist and HSV-2 infects below the waist, but either virus can infect at either locale. Both types of HSV can also persistently infect macrophages and lymphocytes.

Once mucosal epithelial cells are infected (cytolytic infection due to necrosis of infected cells and inflammation response and ballooning of infected cells, production of Cowdry type A intranuclear inclusion bodies), the virus replicates around the lesion and enters into the innervating neurone. The virus travels along the neurone (by a process called retrograde axoplasmic flow) to the ganglion. In the case of herpes infections of the oral mucosa, the virus goes to the trigeminal ganglia, whereas in genital infections the virus invades the sacral ganglia.

When the virus infects neurones it enters into latency. If breakage of latency occurs in these cells, the virus travels back down the nerve axon and recurrence of infection (and therefore symptoms) occurs at the same site as the initial infection. Vesicles containing infectious virus are formed on the muscosa and the virus spreads (ballooning degeneration of intra- epithelial cells). Underlying layer (basal epithelium) is intact. As long as the virus is kept moist it can remain infectious. The vesicle heals and there is usually no scar as a result. The virus is found in the lesions on the skin but can also be present in a variety of body fluids including saliva and vaginal secretions.

Many recurrences asymptomatic (viral shedding in secretions). There are several agents that seem to trigger recurrence, most of which are stress-related, exposure to strong sunlight and perhaps fever can lead to recurrence. Interval between stimulus and appearance of lesion: 2–5 days. Recurrent infections are usually less pronounced than the primary infection and resolve more rapidly.

Pathogenesis EBV infection

Epithelial cells of the oropharynx are the portals of EBV infection. The virus is transmitted primarily by repeated contact with oropharyngeal secretions, and is primarily transmitted by adults 30–50 days or by children 10–14 days following infection. It can be isolated from saliva, blood, and lymphatics. EBV invades B lymphocytes by means of their CD21 receptors; within 18–24 hours, EBV antigens are detectable within the lymphocyte nucleus.

The signs and symptoms of infectious mononucleosis are the result of viral replication and the host immune response to viral antigens. Infected B lymphocytes spread the infection throughout the reticuloendothelial system (e.g., liver, spleen, and peripheral lymph nodes). EBV infection of B lymphocytes results in a humoral and cellular response to the virus. EBV initiates B lym-

phocyte proliferation (plasma cells) and immortalization (memory B lymphocyte) without the role of T-helper cells. EBV is a B-cell mitogen that can cause many B lymphocytes to become antibody-producing plasma cells.

Many of the antibody-producing plasma cells produce antibodies that do not react with EBV antigens. Some of the plasma cells produce antibodies that react with red blood cells from other mammals such as cattle and sheep. This humoral immune response, called the heterophile response, is the basis for the serologic tests used to screen for infectious mononucleosis (e.g., heterophil antibody test [Monospot test]). Other plasma cells produce antibodies that react with EBV antigens and can be used to confirm a diagnosis of infectious mononucleosis. As with many viral infections, the T lymphocyte response is essential in the control of EBV infection; natural killer (NK) cells and predominantly CD8 cytotoxic T cells control proliferating B lymphocytes infected with EBV.

During the acute phase of infectious mononucleosis, as many as 20% of the circulating B lymphocytes will produce EBV antigens, whereas only 1% will produce them during convalescence. The virus usually is not found free in the blood but is present as immune complexes, which may be responsible for the arthralgias and urticarial rashes that occur during the acute phase of the disease.

B lymphocytes that produce complete virions are killed by viral-directed cytolysis, whereas infected B lymphocytes that do not produce complete virions are the target of cytotoxic T cells that control their proliferation. Lymphocytosis associated with infectious mononucleosis is caused by an increase in the number of circulating activated T and B lymphocytes (also known as Downey cells because of their atypical presence in peripheral blood). EBV can be recovered from oropharyngeal washings 12–18 months after the disappearance of circulating Downey cells and the patient has recovered from the illness. Infection with the EBV virus is lifelong.

Pathogenesis CMV infection

CMV encodes a protein, UL16, which is involved in the immune evasion of NK cell responses. It binds to ligands ULBP1, ULBP2 and MICB of NK cell activating receptor NKG2D, which prevents their surface expression. These ligands are normally upregulated in times of cellular stress, such as in viral infection, and by preventing their upregulation, CMV can prevent its host cell from dying due to NK cells.

Congenital cytomegalovirus

Congenital cytomegalovirus is an intrauterine infection, distinct from perinatal cytomegalovirus infection. In perinatal infections, virus is transmitted to the newborn at the time of birth, or shortly after, by way of infected birth canal, breast milk, or blood transfusion. Congenital infection probably results

from virus acquired by susceptible women immediately before or during early pregnancy followed by viremia, placental infection, and hematogenous and transplacental spread to the fetus. Alternative postulated, but unproven, mechanisms include: reactivation of latent virus within uterine tissue, transovarian infection, or spermatozoan infection. Preexisting maternal immunity protects considerably from virus transmission.

Cytomegalovirus can infect many different cell types and all major organs. The cochlea is frequently involved, as is the central nervous system. There is a predilection for periependymal neurons and glia, with focal encephalitis and periependymitis. Necrotic periependymal tissue subsequently calcifies. Calcifications are typically periventricular but may also be scattered throughout the brain. Cytomegalovirus produces cytolysis, with focal necrosis and a localized mononuclear inflammatory response. Tissue damage results from direct effects of the inflammatory response as well as an associated vasculopathy resulting in ischemia and encephalomalacia, immune-mediated reactions, and apoptosis.

Typical pathology involves cytomegalic brain cells with intranuclear inclusions. When cytomegalovirus infects developing CNS tissue, it can produce microcephaly with neuronal migration defects. Severe destructive changes lead to more severe brain abnormalities such as porencephalic cysts, cerebellar hypoplasia, aqueductal stenosis, and hydrocephalus.

Congenital cytomegalovirus is a persistent chronic infection. Half of infected children show viremia for months and viruria for 6 years or more. Cytomegalovirus may be excreted in saliva for 2 to 4 years. Late sequelae reflect this chronic infection of developing tissue. In addition, some abnormalities that are present at birth may not be detectable until the infant is older.

CMV infects a variety of cells, including mononuclear leukocytes and endothelial cells.

During infection, CMV antigens trigger the innate immune system to secrete various antiviral peptides, including interferon. The replication of CMV results in the release of viral nucleic acid intermediaries and viral antigens, which serve as targets for viral detection by a variety of diagnostic assays. The quantification of these viral antigens and nucleic acid intermediates also serves as a means to monitor therapeutic responses.

The recognition of the crucial role of cytotoxic T cells in the control of CMV has led to investigations into the potential clinical utility of CMV-specific T-cell infusion in controlling recalcitrant and drug-resistant CMV diseases.

CLINICAL MANIFESTATIONS

Herpes simplex viral infection

The clinical manifestations of common Herpes simplex virus **(**HSV) infections are vesicles on skin and mucous membranes. Classical infections present with small, 2–4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers.

Acute oropharyngeal infections. Herpes gingivostomatitis is an extremely painful condition with acute onset, pain in the mouth, hypersalivation, refusal to eat or drink, and fever of up to 40,0 °C. The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including on the gums, lips, tongue, palate, tonsils, and pharynx. The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally only present a few days before progressing to form shallow ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy are common. Untreated, the illness resolves in 7—14 days, although the lymphadenopathy may persist for several weeks. In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a health care provider, and signs and symptoms may be indistinguishable from streptococcal pharyngitis with fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes labialis is the most common manifestation of recurrent HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, cheek, or oral mucous membranes. Older patients report itching, or pain 3–6 hr (rarely as long as 24–48 hr) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6–10 days.

Cutaneous infections. In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro- or micro-abrasions and exposure to infectious secretions. HSV infections, an initial cutaneous infection establishes a latent infection that can subsequently result in recurrent

infections at or near the site of the initial infection. Pain, burning, itching, often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then healing without scarring in 6–10 days. While herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. There can be regional lymphadenopathy, recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Genital herpes. Genital HSV infection is common in sexually experienced adolescents and young adults. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatically individuals and also those with asymptomatic or unrecognized infection periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of the pregnant woman, to her newborn. Classical primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or sometimes around the anus or on the buttocks. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles persist for a few days before progressing to the pustular stage and then crusting.

Patients may develop urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge and men a clear mucoid urethral discharge. Significant local pain and systemic symptoms including fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classical primary genital herpes, from onset to complete healing, is 2–3 wk.

Ocular infections. HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2–3 weeks.

Central nervous system infections. HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may present with nonspecific findings, including fever, headache, rigidity of occipital muscles, nausea, vomiting, alteration of

consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal symptoms. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration.

Perinatal infections. Neonatal HSV infection is almost never asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with intrauterine infection typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those that do generally have severe complications. Infants infected during delivery or postpartum present with 1 of 3 patterns of disease: 1) disease localized to the skin, eyes, or mouth; 2) encephalitis with or without skin, eye, or mouth; 3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin.

Varicella zoster virus (VZV)

In small babies VZV infection has clinical manifestation of Chicken Pox.

In adults present clinical manifestation of herpes zoster infection. The lesions of herpes zoster begin as papules, but progress within hours to clear vesicles surrounded by erythema. Vesicles are often oval, with the long axis parallel to skin creases, and are commonly pruritic. New lesions appear progressively over 5–7 days. The head and upper trunk are affected first and most densely, whereas the limbs have fewer lesions and these appear later. A crust then forms from this center outward, and falls off after about 5 days. Prodromal symptoms of malaise, headache and loss of appetite are mild and more common in adults. Unless secondary infection of the skin has occurred, scarring is limited to faint, pale outlines. Indicators of severe disease include confluence of the rash, multiple lesions in the mouth, pharynx, esophagus, trachea and mucosa of the genital tract. Herpes zoster is heralded by pain in the dermatome served by the affected sensory root. Groups of papules then appear at the sites where the cutaneous nerves reach the skin. The skin eruption will be restricted to one dermatome unilaterally in the immunocompetent host; in the immunocompromised patient multidermatomal skin eruptions or generalization may occur. The papules progress to vesicles, pustules and crustae but, unlike varicella, lesions may become confluent and form large, flaccid bullae that rupture to leave weeping bare areas. Uncomplicated lesions can heal in 4–

6 days, but severe rashes may take 3–5 weeks. Nevertheless, skin depigmentation is often the only sequel. Scarring is rare.

Infectious mononucleosis

The incubation period is approximately 4 to 6 weeks. Infection is often heralded by 3 to 5 days of mild headache, malaise, and fatigue. These symptoms are typically followed by the onset of fever, lymphadenopathy, and severe sore throat. The disease in children is generally mild; in adults, it is more severe, with a more protracted course. Major clinical manifestations include fever, sore throat/pharyngitis, and lymphadenopathy; hepatosplenomegaly, jaundice, and rash are also commonly seen.

Body temperature usually rises to 39,4 °C and gradually falls over a variable period averaging 6 days. In severe cases, it is not unusual for temperature to range between 40 °C and 41 °C for 2 weeks or more. Younger children are more likely to be afebrile or have only minimal temperature elevation.

Generalized lymphadenopathy is a typical clinical manifestation of infectious mononucleosis. Shortly after the onset of illness, lymph nodes rapidly enlarge. Any group of lymph nodes can be enlarged, but anterior and posterior cervical lymphadenopathy is most common. The nodes are usually single, tender, 2 to 4 cm in diameter, and not matted. Mesenteric lymphadenopathy can be confused with acute appendicitis. The lymph node enlargement gradually subsides over a period of days to weeks, depending on the severity and extent of involvement.

Sore throat is the cardinal symptom of infectious mononucleosis. The tonsils are usually enlarged, reddened, and covered with exudate in more than 50% of patients. Pharyngitis caused by EBV can be indistinguishable from that caused by group A streptococci. Petechiae appear on the soft palate between days 5 and 17 of illness in up to 25% of patients with infectious mononucleosis. From 6 to 20 lesions are usually seen, characteristically at the junction of the hard and soft palate; they usually become brownish in color within 2 days and then fade.

Moderate enlargement of the spleen occurs in approximately 50% of cases between the second and third weeks of illness. In rare instances, enlargement is followed by trauma-induced or (less commonly) spontaneous rupture leading to hemorrhage, shock, or death. Splenic rupture should be suspected in any patient with acute infectious mononucleosis in whom abdominal pain and signs of peritoneal irritation, hemorrhage, or shock develop; splenic enlargement alone is usually asymptomatic. Once splenomegaly is detected, repeated splenic examination should be avoided. The triad of lymphadenopathy, splenomegaly, and exudative pharyngitis in a febrile patient is typical, but not pathognomonic of infectious mononucleosis, usually that caused by EBV.

Hepatomegaly is present in only 10% to 15% and hyperbilirubinemia in 25%, moderately elevated serum concentrations of hepatic transaminases are found in more than 80% of patients. Jaundice develops in less than 5% and is usually mild; direct hyperbilirubinemia is typical. Hepatitis may be associated with anorexia, nausea, and vomiting.

The incidence of dermatitis in cases of infectious mononucleosis ranges from 3% to 19%. The rash is usually located on the trunk and arms; rarely, palmar dermatitis occurs. Rash appears during the first few days of illness, lasts 1 to 6 days, and can be erythematous, macular, papular, or morbilliform. Sometimes, a urticarial eruption or acrocyanosis is observed. Rarely, the rash can be petechial, vesicular, or hemorrhagic. In some cases patients with infectious mononucleosis has rash after using ampicillin. The rash is copper colored and appears mainly over the trunk. It can develop into an extensive, confluent, maculopapular pruritic eruption that includes the palms and soles. It can persist for up to 1 week, with desquamation occurring over a span of several more days. The rash can also occur with ampicillin derivatives such as amoxicillin and other penicillins such as methicillin. Rash does not represent hypersensitivity to ampicillin, which can be used safely when the infection subsides.

Neurologic conditions attributed to EBV infection have included aseptic meningitis, encephalitis, optic neuritis, cranial nerve palsy, transverse myelitis, acute cerebellar ataxia, subacute sclerosing panencephalitis, psychosis, and central nervous system lymphoma.

Cytomegaloviral infection

The signs and symptoms of CMV infection vary with age, route of transmission, and immunocompetence of the patient. The infection is subclinical in most patients. In infants and young children, primary CMV infection occasionally causes pneumonitis, hepatomegaly, hepatitis, and petechial rashes. In older children, adolescents, and adults, CMV may cause mononucleosis-like syndrome characterized by fatigue, malaise, myalgia, headache, fever, hepato-splenomegaly, elevated liver enzymes, and atypical lymphocytosis. The course of CMV mononucleosis is generally mild, lasting 2–3 wk. Clinical presentations may include occasionally persistent fever, overt hepatitis, or a morbilliform rash. Recurrent infections are asymptomatic in the immunocompetent host.

Immunocompromised Persons. The risk for CMV disease is increased in immunocompromised persons, with both primary and recurrent infections. Illness with a primary infection includes pneumonitis (most common), hepatitis, chorioretinitis, gastrointestinal disease, or fever with leukopenia as isolated entities or as manifestations of generalized disease, which may be fatal. The risk is greatest in bone marrow transplant recipients and in patients with AIDS. Pneumonia, retinitis, and involvement of the central nervous system and

gastrointestinal tract are usually severe and progressive. Submucosal ulcerations can occur anywhere in the gastrointestinal tract and may lead to hemorrhage and perforation. Pancreatitis and cholecystitis may also occur.

Congenital infection. Symptomatic congenital CMV infection was originally termed cytomegalic inclusion disease. Only 5% of all congenitally infected infants have severe cytomegalic inclusion disease, another 5% have mild involvement, and 90% are born with subclinical, but still chronic, CMV infection. The characteristic signs and symptoms of clinically manifested infections include intrauterine growth restriction, prematurity, hepatosplenomegaly and jaundice, blueberry muffin-like rash, thrombocytopenia and purpura, and microcephaly and intracranial calcifications. Other neurologic problems include chorioretinitis, sensorineural hearing loss, and mild increases in cerebrospinal fluid protein. Symptomatic newborns are usually easy to identify. The most severe symptomatic congenital infections and those resulting in sequelae are more likely to be caused by primary rather than reactivated infections in pregnant women. Reinfection with a different strain of CMV can lead to symptomatic congenital infection. Asymptomatic congenital CMV infection is likely the leading cause of sensorineural hearing loss, which occurs in approximately 7% of all infants with congenital CMV infection, whether symptomatic at birth or not.

Perinatal infection. Infections resulting from exposure to CMV in the maternal genital tract at delivery or in breast milk occur despite the presence of maternally derived, passively acquired antibody. Approximately 6–12% of seropositive mothers transmit CMV by contaminated cervical-vaginal secretions and 50% by breast milk to their infants, who usually remain asymptomatic and do not exhibit sequelae. Occasionally, perinatally acquired CMV infection is associated with pneumonitis and sepsis-like syndrome. Premature and ill full-term infants may have neurologic sequelae and psychomotor retardation. However, the risk for hearing loss, chorioretinitis, and microcephaly does not appear to be increased. Premature infants with transfusion-acquired CMV infection have a much greater risk for morbidity.

Human herpes virus (HHV) 6 type

Roseola infantum. Roseola is a mild febrile, exanthematous illness occurring almost exclusively during infancy. More than 95% of roseola cases occur in children younger than 3 yr, with a peak at 6–15 mo of age. Transplacental antibodies likely protect most infants until 6 mo of age.

Infants with classic roseola exhibit a unique constellation of findings displayed over a short period of time. Consequently, classic roseola is infrequently confused with other childhood exanthems.

The prodromal period of roseola is usually asymptomatic but may include mild upper respiratory tract signs, among them minimal rhinorrhea, slight pharyngeal inflammation, and mild conjunctival redness. Mild cervical or, less frequently, occipital lymphadenopathy may be noted. Some children may have mild palpebral edema. Physical findings during the prodromal stage have no clear relationship to roseola, and may simply reflect an accompanying respiratory viral infection. Clinical illness is generally heralded by high temperature, usually ranging from 37,9 to 40 °C, with an average of 39 °C. Some children may become irritable and anorexic during the febrile stage, but most behave normally despite high temperatures. Seizures may occur in 5–10% of children with roseola during this febrile period. Infrequent complaints include rhinorrhea, sore throat, abdominal pain, vomiting, and diarrhea. Fever persists for 3–5 days, and then typically resolves rather abruptly ("crisis"). Occasionally, the fever may gradually diminish over 24–36 hours ("lysis"). A rash appears within 12–24 hr of fever resolution. In many cases, the rash develops during a few hours of fever resolution. The rash of roseola is rose colored, as the name implies, and is fairly distinctive. However, it may be confused with exanthems resulting from rubella, measles at al. The roseola rash begins as discrete, small (2–5 mm), slightly raised pink lesions on the trunk and usually spreads to the neck, face, and proximal extremities. The rash is not usually pruritic, and no vesicles or pustules develop. Lesions typically remain discrete but occasionally may become almost confluent. After 1–3 days, the rash fades.

Fever in infants without classic roseola. HHV-6 account for a significant proportion of nonspecific febrile illnesses, without a focus of infection, in infants. Approximately 15% of febrile infants presenting to hospital emergency room have primary HHV-6 infection.

Central nervous system infections. HHV-6 is neurotropic and can invade the CNS. Primary HHV-6 infection is responsible for approximately 10–20% of febrile seizures in infants. Most of these children do not subsequently experience a rash. HHV-6 is associated with rare cases of encephalitis and meningoencephalitis, mostly occurring in immunocompromised patients. HHV-6 DNA is present in cerebrospinal fluid from 6% of children and adults with focal encephalitis of unknown cause.

Mononucleosis-like illness and hepatitis. Several mononucleosis-like infections associated with HHV-6 have been reported in adults. HHV-6 may rarely cause clinical symptoms of hepatitis. There is controversy regarding the association of HHV-6 with some cases of fulminant liver failure in infants.

Diagnosis of HSV Infections

In HSV infections CBC characterized by lymphomonocytosis, at Infectious mononucleosis –leukocytosis, lymphomonocytosis, atypical lymphocytes (Downey cells or virocytes) and increased ESR.

Most infections are asymptomatic and therefore go undiagnosed. There are fluorescent antibody and ELIZA tests.

Cytological - multinucleated (cytomegalinic) cells with characteristic inclusions can be seen in biopsies of many tissues.

There are also **serological tests** available. Heterophile antibodies are produced by the proliferating B cells and these include an IgM that interacts with Paul-Bunnell antigen on red blood cells.

Virus can be isolated from biopsy specimens, that is from the lesions, and grown on tissue culture cells where it forms characteristic cytopathic effects (plaque) including multinucleated cells. The presence of anti-HSV antibodies in the patient can be used to form a diagnosis of the primary infection but recurrence is not usually accompanied by a rise in antibody levels.

Herpes viral culture. Cells or fluid from a fresh sore are collected with a cotton swab and placed in a culture cup. A viral culture is the best method of identifying a genital herpes infection. But the culture often fails to find the virus even when it is present (false-negative results).

Herpes virus antigen detection test. Cells from a fresh sore are scraped off and then smeared into a microscope slide. This test finds markers (called antigens) on the surface of cells infected with the herpes virus. This test may be done with or in place of a viral culture.

Polymerase chain reaction (PCR) test. A PCR test can be done on cells or fluid from a sore or on blood or on other fluid, such as spinal fluid. PCR finds the genetic material (DNA) of the HSV virus. This test can tell the difference between types HSV.

Antibody tests. Blood tests can find antibodies that are made by the immune system to fight a herpes infection. Antibody tests are sometimes done but are not as accurate as a viral culture at finding the cause of a specific sore or ulcer. Antibody tests cannot tell the difference between a current active herpes infection and a herpes infection that occurred in the past. Because antibodies take time to develop after the first infection, you may not have a positive antibody test if you have just recently been infected. Some blood tests can tell the difference between types HSV.

TREATMENT

Treatment of herpes virus infection (HVS-1,2)

I. Orolabial herpes

1. General regimen
2. Diet (without allergens, food shouldn't be cold)

In the treatment of primary orolabial herpes you should prescribe oral Acyclovir, in a dosage of 200 mg five times daily for five days for adults and 5 mg/kg 3 times a day, accelerates loss of crusts by one day and Zovirax Ointment (apply to affected skin 4–5 times a day). Standard analgesic therapy with acetaminophen or ibuprofen, careful monitoring of hydration status and aggressive early rehydration therapy are usually sufficient to avoid inpatient admission in most children.

II. Genital Herpes

1. General regimen
2. Diet (without allergens)

Antiviral therapy is recommended for an initial genital herpes outbreak, especially if the patient has systemic symptoms or is immunocompromised. Oral acyclovir is effective in reducing symptoms. Intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.

The oral Acyclovir dosage for treatment of primary or initial nonprimary genital herpes is 200 mg five times daily for 10 days. Valacyclovir, 500 mg should give twice daily 5–10 days, is indicated for the treatment of primary genital herpes but it costs more than acyclovir.

Besides standart antiviral therapy, for patients with recurrent HSV infection treatment necessary prescribe drugs (herbs and supplements) which do immune system stronger.

Herbs and Supplements

- Echinacea (Echinacea purpurea) 1 tabl. 34 times a day
- Siberian ginseng (Eleutherococcus senticosus) 15–40 drops 1 time a day
- Zinc (5–20 mg 1 time a day)
- Flavanoid glicozids: Proteflazid scheme in adults: 1 week – 5 drops 3 times a day; 2–3 weeks – 10 drops 3 times a day; 4 week – 8 drops 3 times a day

Prevention

- Hygiene is important. Avoid touching the sores. Wash hands frequently during the day. Fingernails should be scrubbed daily. Keep the body clean.
- Avoid tight-fitting clothing, which restricts air circulation and slows healing of the sores.
- Choose cotton underwear, rather than synthetic materials.

- Wearing sun block helps prevent sun-triggered recurrence of herpes simplex virus 1 (HSV-1).

– *Use a latex condom* (While condoms may not provide 100% protection, they have been proven to significantly reduce the risk of sexual disease transmission)

– *Limit the number of sexual partners*

Herpes and Pregnancy

Pregnant women who have genital herpes due to either herpes simplex virus 2 (HSV-2) or herpes simplex virus 1 (HSV-1) have an increased risk for miscarriage, premature labor, inhibited fetal growth, or transmission of the herpes infection to the infant either in the uterus or at the time of delivery. Herpes in newborn babies (herpes neonatalis) can be a very serious condition.

The reasons for the higher risk with a late primary infection are: during a first infection, the virus is shed for longer periods, and more viral particles are excreted, an infection that first occurs in the late term of pregnancy does not allow the mother time to develop antibodies that would help her baby fight off the infection at the time of delivery.

The risk for transmission also increases if infants with infected mothers are born prematurely, if there is invasive monitoring, or if instruments are used during vaginal delivery. Transmission can occur if the amniotic membrane of an infected woman ruptures prematurely, or as the infant passes through an infected birth canal. This increased risk is present if the woman is having or has recently had an active herpes outbreak in the genital area.

Very rarely, the virus is transmitted across the placenta, a form of the infection known as congenital herpes. Also rarely, newborns may contract herpes during the first weeks of life from being kissed by someone with a herpes cold sore.

Infants may get congenital herpes from a mother with an active herpes infection at the time of birth. Aggressive treatment with antiviral medication is required, but it may not help systemic herpes.

Treatment of infectious mononucleosis

Treatment of mononucleosis depends on clinical form and severety of the disease.

Regimen – bed rest

- Diet (№ 5)
- Antiviral therapy: Acyclovir 200 mg 1 time a day, Valavyr 500 mg 1 time a day
- Antibiotics – Cefalosporins of 3 and 4 generations: Cefalexin, Cefasolin, cefuroxim **(Contraindications** – to use Ampicillin)
- Drugs, which improve immune system

- Antihistamynic drugs (Loratadin 5-10 mg 1 time a day)
- Antipyretics (Paracetamol 10–15 mg/kg or tabl. 500 mg, Nurofen 50–125 mg)
- Infusion therapy (solutions of Glucose 5%, NaCl 0,9%, Rheopolyglukinum 5–10 ml/kg)
- At severe cases: Corticosteroids – Prednisolon 1–2 mg/kg;

Treatment of CMV infection depends on concrete clinical form and severity. Antiviral therapy: Ganciclovir is preparat from group Aciklovir, you should prescribe it on 5 mg/kg each 12 hours 14–21 days intravenously. Oral (taken by mouth) Ganciclovir may be used to prevent CMV disease.

– Regimen – bed rest

– Diet (№ 5)

– Ganciclovir is preparat from group aciklovir, you should prescribe it on 5 mg/kg

– Inosine pranobex 50 mg/kg (for adults and for children more than 3 years old) 3 courses for 5–10 days

Infusion therapy (5%Glucose, NaCl 0,9%, Reopoliglukin 5–10 ml/kg)

Prevention of mononucleosis and CMV

- wash your hands thoroughly after contact with urine or saliva
- avoid oral contact with saliva or objects covered with saliva (such as cups, pacifiers, toys, etc.)
- test of preparates of blood to transfusion on EBV and CMV.

Навчальне видання

ГЕРПЕСВИРУСНАЯ ИНФЕКЦИЯ У ДІТЕЙ

Методичні вказівки до практичних занять для студентів V–VI курсів

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Manual for practical lessons
for the V–VI year students