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Infections in children

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PERSISTENT HERPESVIRUS INFECTIONS AND THEIR ROLE IN THE MORBIDITY OF CHILDREN FROM THE GROUP WITH FREQUENT AND LONG-LASTING DISEASES

Summary. *The study analyzes data on the role of herpesvirus persistent infections in the recurring course of respiratory diseases in children with frequent and long-lasting diseases. Approaches to etiopathogenetic therapy and rehabilitation with the use of flavonoids are considered.*
Key words: *herpesvirus infections, children, respiratory diseases, treatment, Proteflazid, Flavozid®.*

According to the analysis carried out by WHO experts, distinctive characteristic of the health status of the population in the world is a state of decreased immunoreactivity: according to different sources, up to 50-70% of people have signs of immunity disorders. The consequence of this is an increase in the incidence of diseases caused by a conditionally pathogenic, opportunistic microbiota that persists for a long time or permanently in the body and often causes various pathological conditions - chronic inflammatory process, allergic, autoimmune and oncological diseases [1]. Persistent infections include a number of infectious agents that differ in nature (viruses, bacteria, protozoa), the method of penetration (transplacental, intranatal, sexual, respiratory, etc.), pathogenicity (absolutely or conditionally pathogenic), the nature of the host's immune response.

At the same time, persistent infections unite common characteristics, in particular, *mainly the intracellular activity of pathogens with the use of the host's cellular resources and, as a consequence, the difficulty of their extermination; duration (persistence) of the effect on immunocompetent cells; "slow" flow; ability to continuously or cyclically multiply (replicate under the influence of various unfavorable factors) in infected cells of different tissues - leukocytes, tissue macrophages, monocytes, endothelium, epithelial cells, fibroblasts, cardiocytes, neurocytomas, hepatocytes, causing in them not only dystrophic, but also destructive processes and creating at the same time a constant threat of the development of an infectious-inflammatory process. They are distinguished by the minimal effect of the majority of anti-infectious agents - antibiotics, antiviral drugs, immunoglobulins, etc. As a consequence, the host's immune factors can damage the infected cells along with the infectious agents. Therefore, an immune response to a persistent infectious agent can be accompanied not only by a protective, but also by a damaging effect: immune responses from the host can destroy his affected cells.*

At the beginning of the 20th century, a leading role belonged to infections of bacterial nature (scarlet fever, diphtheria, pertussis, dysentery). In the second half of the XX century and at the beginning of the 21st century, infectious diseases of the viral etiology (influenza, ARVI, enterovirus, rotavirus, herpetic infections, HIV infection, hepatitis, etc.) already dominate. Among the persistent intracellular agents under consideration, the herpesvirus group occupies a leading place both in the prevalence and in the width of the pathological processes caused. *Today, the infection with herpes viruses and the associated morbidity in the general population outpaces the rate of population growth of the Earth.* According to the WHO, the determining place among infectious pathology will be occupied by the herpetic infection in the future. This is due to the variety of clinical manifestations, the characteristics of pathogens and the possibility of their spread in practically all known ways.

The World Health Organization warns the world community about the danger of a latent pandemic of herpetic infection. According to WHO, 70 to 90% of the world's population is infected with one or more types of herpes virus and 50% of them have relapses every year due to lack of stable immunity. Herpesviruses as the cause of death take second place after the flu - more than 15% of cases [2, 3]. In the US, 1.6 million young women each year get genital herpes caused by type 2 herpes simplex virus (HSV), and more than 2% of pregnant women have a seroconversion to it during pregnancy. The National Conference on the Prevention of Sexually Transmitted Infections, which was held in March 2012 in Minneapolis, USA, published alarming data: mortality in herpetic infection in newborns reaches 30%, and 20% of surviving children have nervous system lesions. The incidence of this disease in the United States is 8-60 cases per 100,000 births. It is the future mother that is the main source of infection for the fetus and newborn [4-6]. There are data that by the age of 5 about 60% of children have already been infected with herpes viruses, and by the age of 15 their share is 90%. Most people are lifelong virus carriers. And in 85-100% of cases the primary infection in them proceeds asymptomatically and only in 1-15% in the form of a systemic infection [7].

Herpesviruses can affect almost all organs and systems of a person, causing acute, chronic and latent forms of infection. According to the World Information Bank forecasts, herpes-viral infections and diseases caused by them are defined as "the global problem of mankind" for the foreseeable future. ***Herpesviridae*** viruses are especially important in connection with their ubiquitous spread on the Earth and lifelong infection of people at any age. Some specialists even use the term "herpetic disease", emphasizing polytropic nature of the herpesviruses.

It is assumed that about 25 million people are infected each year in the CIS with various forms of herpetic infections (HI). Analysis of the annual incidence of HI indicates that 15% of the population have herpetic lesions of the skin and mucous membranes, genital herpes occurs in 6-10% of the adult population, more than 2% have nervous system lesions, during which residual effects are observed for a long time in 14-30% of the cases (up to disability), with a mortality rate of 5-70%, depending on the clinical form of the lesion of the central nervous system [8].

Herpesvirus infections are the most common cause of acute viral encephalitis (up to 20%) with a mortality rate of up to 30%. In almost all cases, they are caused by type I HSV. It should be noted that the course of aphthous stomatitis in infants and young children, accompanied by febrile fever, indicates an infection caused by viruses of the herpes family. Data are presented that intrauterine herpesvirus infections play a leading role in the formation of a contingent of sickly children [9, 10].

The importance of herpesviruses in the involvement of the eyes (ophthalmoherpes) is high, and in almost half of the patients the disease leads to the development of cataracts or glaucoma. Long-term herpetic infections have a pronounced suppressive effect on immunity and cause prolonged antigenic irritation of the lymphoepithelial tissue of the nasopharynx of the child.

By following one's own, individual for each type and strain of the virus, biological rhythm or under the influence of external causes, herpesviruses begin to reproduce, enter the lymph and hemocirculation, and come in contact with the perceiving mechanisms of the immune system. The latter responds to this biological challenge with a standard immune response: interferons are produced, specific antiherpetic antibodies, cytokines, etc. However, the biological evolution of herpesviruses has given them a phenomenal ability in the active reproduction phase to produce proteins that block the receptors of lymphocytes that coordinate and guide the immune response, which in some circumstances leads to a delay and chaos of the antiherpetic immune response and the development of the disease.

An important characteristic of herpesviruses is the ability, after primary infection in childhood, to persist for life in the body and reactivate under the influence of various exo- and endogenous provoking factors. Herpesvirus infection is best characterized by a single figurative expression: “Being infected once means being infected for life”. Emerging in response to the herpes viruses infiltration, specific antibodies often do not ensure the sanation of the body from viruses and often do not prevent the recurrence of the disease. In this regard, the tasks of timely diagnosis of infection and determining the activity of its course are set for practicing doctors - obstetricians, pediatricians, therapists - in the first place. Correct evaluation and interpretation of the obtained results of clinical, specific laboratory and instrumental research enables to take adequate and safest medical and rehabilitation measures for infected and sick people - a pregnant woman, fetus, child, adult patient.

Herpes viruses are now clearly classified and integrated into the extensive Herpesviridae family. The Herpesviridae family includes more than 100 representatives, 8 of which are the most pathogenic for humans (human Herpes virus - HHV). The possibility of affect by the Herpes virus of the group of the

child's organs and tissues is extensive, and predicting the point of their application is quite difficult (Table 1).

In the course of 15 years of research conducted in our clinic, a lot of data on the nature and direction of the effect of Herpes viruses on the child's organism, on their influence on the development of pathological processes in various organs and systems - bronchopulmonary, cardiovascular, etc., including Formation of a contingent of children with frequent and long-lasting diseases (CwFLLD) were obtained.

Table 1. Specificity of involvement in the course of acute and recurrent Herpes virus diseases in humans

Herpes virus type	Synonyms	Primary diseases	Recurrent diseases
Sub-family of *Alphaherpesvirinae* (α-Herpes viruses)			
Herpes simplex virus Type I (HSV-1, HHV-1)	Herpes simplex, herpes catarrhalis	Oral-facial lesions, aphthous-ulcerative stomatitis, labial herpes, herpetic dermatitis, herpetiform eczema, keratitis, conjunctivitis, pneumonitis, encephalitis	Oral herpes, kerato-conjunctivitis, encephalitis
Herpes simplex virus Type II (HSV-2, HHV-2)	Genital herpes	Genital herpes, neonatal herpes, disseminated herpes, meningitis	Genital herpes
Varicella zoster virus, Human herpes virus Type 3, VZV, HZV, HHV-3	Shingles, Herpes zoster	Varicella disseminated	Shingles involvement in the course of sensitive nerve endings, pre- and perinatal infection, disseminated infection during immunodeficiency
Sub-family of *Betaherpesvirinae* (β-Herpes viruses)			
Cytomegalovirus, Human herpes virus Type 5 - CMV, HHV	Cytomegaly	Pre- and perinatal infection, teratogenic effect, congenital anomalies, outcomes of chronic inflammatory involvement of the heart, brain, kidney, liver, pancreas in the process of intrauterine infection, cytomegaly in immunodeficiency, immunodeficiency, involvements of liver, kidney, lung, eye, lymph nodes, CNS. Liability to infection generalization.	Cytomegaly in patients after organ transplantation, retinitis, colitis, pneumonia, carditis, hepatitis or neuroinfections in the course of AIDS
Human herpes virus Type 6 - HHV-6	Human B lymphotropic virus	Rose rash of infants (erythema of newborns), chronic fatigue syndrome and immune depression, mononucleosis-like syndrome	Chronic fatigue syndrome, encephalomyelitis, cofactor of HIV infection, of oral and cervical carcinoma, systemic diseases after transplantation
Human herpes virus Type 7 - HHV-7		Rose rash of infants	Chronic fatigue syndrome
Sub-family of *Gammaherpesvirinae* (γ-Herpes viruses)			
Kaposi's sarcoma associated herpes virus, Human herpes virus Type 8, KSHV, HHV-8	Human B lymphotropic virus		Kaposi's Sarcoma, primary disseminated lymphoma

In the process of management of children with frequent and long-lasting diseases the reasons for the development of this condition usually are not taken into account, and a large number of medications, including salicylates and antibiotics are widely and often unjustifiably used in their treatment.

Our examination data of 140 sickly infants [11,12] indicate the high incidence of their infection with herpes viruses. Specific IgG to herpes viruses are detected in more than 80% of cases: to cytomegalovirus (CMV) - 73%, to Epstein-Barr virus (EBV) - 72.2%, to HSV - 4%. Moreover, the active course of the infectious process, which was more often observed in children with clinical manifestations of the ARI event, was found in more than 75% of infected patients: the DNA of the Epstein-Barr virus was detected in 55.8% of children, CMV in 67.4%, at this time in 40,1% of patients their combination was detected.

The importance of herpesviral infections for the formation of the child's frequent diseases syndrome is indicated by high rates of frequency, duration and number of complications of ARI in infected children. Children of this group were more likely to have acute respiratory viral infection than uninfected and occasionally ill, respectively 8.10 ± 2.68; 6,30 ± 2,34 and 4,83 ± 0,12 events of ARVI per year. At the same time, the duration of the acute respiratory disease event was 13.10 ± 2.26, respectively; 10.80 ± 3.21 and 5.80 ± 1.38 days.

The special characteristic of the course of respiratory diseases in infected children with frequent and long-lasting diseases is the high proportion of complications. In case of occasionally ill children, complications (average otitis media, etmoiditis, bronchial obstruction syndrome, stomatitis, pneumonia, urinary tract infection) occurred in 19.6% of cases in ARVI, in 71.0% in those infected with herpesviruses - in 71.0%, in uninfected - in 45.6% of cases.

In the study of pathogenetic mechanisms of the formation of an increased respiratory incidence in infected with herpesviral infections of the lungs, an imbalance is revealed in practically all parts of the immune system. There was a significant increase in the levels of mature T-lymphocytes and their suppressor-cytotoxic fraction, which is typical for the immune response in the process of viral replication, and a pronounced natural killer deficiency caused by the ability of herpesviruses to block receptors of monocytes expressing activation molecules of the killer fraction of lymphocytes. The expressed disbalance of the humoral link was indicated by hyperproduction of immunoglobulins (A, M and G) associated with a decrease in the level of mature B-lymphocytes.

The obtained data enable us to consider the immune disorders caused by herpesvirus infections as a determining factor of the pathogenesis of recurrent respiratory diseases in children with frequent and long-lasting diseases. The pronounced stimulation of the suppressor-cytotoxic link of T-lymphocytes along with hyperimmunoglobulinemia indicates activation of these parts of the immune system in response to the persistence of the infectious agent. Since the link of natural killers is one of the main elements in primary contact with viral infections, its insufficiency, which reaches its maximum in children of this category, may be the main factor of increased morbidity of ARI.

The mechanisms of formation of the persistent state also correlate with changes in the phagocytic link: a decrease in the number of active phagocytes (46.30 ± 2.35 in infected children with frequent and long-lasting diseases versus 50.60 ± 3.51 in uninfected and 51.10 ± 4.21 with occasionally ill children) testifies to the inhibitory effect of persistent infections, which is also confirmed by the suppression of their digestive function (the rate of phagocytosis completion is almost 30% lower). Changes in the phagocytic link also explain the high proportion of bacterial complications in infected children with frequent and long-lasting diseases. The pronounced immune imbalance of herpesvirus-infected children with frequent and long-lasting diseases is also confirmed by changes in the cytokine status. Characteristic for these children is a decrease in the level of a-interferon (up to 8.20 ± 1.26 pg/ml compared to 13.20 ± 3.21 pg/ml in uninfected children), which is a factor in the implementation of reduced anti-infection protection.

As etiotropic therapy to suppress the reproduction of herpes viruses, flavonoids with a powerful antiviral effect are widely used. So, antiviral drug Proteflazid developed in Ukraine, as a highly effective antiherpetic drug, is used in our country and abroad since 2002 [13-24]. Its active substances are flavonoids, obtained from wild cereals Deschampsia caespitosa L. and Calamagrostis epigeios L. (tufted hair grass and bushgrass).

For the treatment of infants, a 2% Proteflazid solution, **Flavozid®**, is used. This alcohol-free form of Proteflazid in syrup form can be prescribed to children since birth [23, 25]. It does not contain dyes, flavors, sugar, it is nontoxic, well tolerated by children with a burdened allergological anamnesis.

In the case of replicative form (active course) of herpesvirus infections **Flavozid®** is assigned by us for 3 months. With an increase in the incidence rate of acute respiratory infections 6-9 months after the complex of differentiated etiopathogenetic therapy due to the possible activation of herpetic infections, repeated use of the drug at the age-appropriate dosage within 3 months is recommended. In the severe course of herpesviral infections, we have experience with **Flavozid®** (Proteflazid) up to 6-12 months without formation of refractory and any side effects [26].

We have demonstrated the high antiviral efficacy of **Flavozid®** in the treatment of 65 children with frequent and long-lasting diseases infected with herpes viruses. The results of the treatment were compared with the data of 35 children with frequent and long-lasting diseases, also infected with herpesviral infections, but receiving a conventional therapy for ARI (according to the order of the Ministry of Healthcare of Ukraine No. 354 of 09.07.04).

Observing the patients after the course of rehabilitation using **Flavozid®** demonstrates that after 3 months of therapy in infected with herpes viruses children with frequent and long-lasting diseases significantly (almost 1.5 times) decreased the incidence of ARI during the year and 1.4 times decreased the rate of complications. Further study in a long-term follow-up (up to 12 months) in children with frequent and long-lasting diseases receiving **Flavozid®** showed a 3-fold decrease in the incidence of acute respiratory disease, a 1.5-fold reduction in the time of event of the disease, and a 35% reduction in complication rates, along with normalization of immunity indices. In connection with the increase in the incidence rate at the 6th month of follow-up due to the reactivation of intracellular pathogens, the need to conduct a repeated course of complex etiopathogenetic therapy 2 times a year with 6-month interruptions was determined [26,27]. Identical results were obtained in the pulmonology department of the Republican Specialized Scientific and Practical Medical Center for Pediatrics of the Ministry of Healthcare of Uzbekistan [28].

Morbidity of acute respiratory infections of infected children with frequent and long-lasting diseases, who received conventional therapy, decreased by 1.2 times during the following year, with the remaining duration of the event of the disease and the number of complications.

Flavozid® [26] is taken 20-30 minutes before meals. For herpes virus infections in children, the drug was administered by us as follows:

- children under 1 year - 0.5 ml 2 times a day;
- children from 1 to 2 years - 1 ml 2 times a day;
- children from 2 to 4 years: 1st week - 1.5 ml 2 times a day; starting from the second week - 3 ml 2 times a day;
- children from 4 to 6 years: 1st week - 3 ml 2 times a day; starting from the second week - 4 ml 2 times a day;
- children from 6 to 9 years: 1st week - 4 ml 2 times a day; starting from the second week - 5 ml 2 times a day;
- children from 9 to 12 years: 1st week - 5 ml 2 times a day; starting from the second week - 6 ml 2 times a day;
- children over 12 years and adults: 1st week - 5 ml 2 times a day; starting from the second week - 8 ml 2 times a day.

The duration of administration of **Flavozid®** (Proteflazid) in children with frequent and long-lasting diseases is up to 3-4 (if necessary, up to 12 months) and depends on the agent detected (the longest course, 4-6 or more months, is necessary to suppress replication in chronic recurrent infections caused by cytomegalovirus and Epstein-Barr virus), as well as from disorders in the somatic and immunological status of patients, the frequency and severity of clinical manifestations and relapses [26].

Thus, herpesviral infections cause not only an acute infectious process with toxic damage to the cellular structures of various organs and tissues, but even in latent flow, they contribute to changes and disorders of the immune response, determine the development of chronic inflammatory diseases, play a major role in the recurring course of respiratory diseases in children from the group of children with frequent and long-lasting diseases. The use of the flavonoid drug **Flavozid®** (Proteflazid) in the complex treatment and rehabilitation of children of this category, which has direct antiviral and immunotropic action, significantly reduces the number of events of respiratory diseases, their duration and the number of complications.

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