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LONG-TERM SUBFEBRILITY IN CHILDREN. POSSIBLE CAUSES AND APPROACHES TO TREATMENT

E.I. Yulish, O.E. Chernysheva, Yu.L. Soroka
M.Gorky Donetsk State Medical University pp. 67-72

Summary. *The role was investigated of herpesviral infections in the development of low-grade pyrexia in children. The principles of treatment of children infected with herpesviruses were defined.*
Key words: *low-grade pyrexia, herpesviral infections, children, Flavozid.*

The presence of long-term subfebrility in a child is a not infrequent and a serious enough reason of appealability to pediatric physician. In this case, certain difficulties may emerge during investigation of the cause of such condition and selection of adequate disease management, accordingly.

The term "subfebrile" derives from words sub — "under, to a weak extent" and febris — "fever" and literally means "under-feverish", "with a little hyperpyrexia". It corresponds to axillary temperature from 37.0° to 38.0°C, rectal temperature is by 0.5°-1.0^0 C higher than that of skin. It is said about long-term subfebrility in the event if axillary temperature at the level from 37.0°C to 38.0°C is being registered during 3 weeks at least [2].

The major reasons of subfebrility in children are:

— infectious diseases;
— chronic infection loci in the internal parts of body;
— intoxications (poisoning);
— helminthic invasions;
— metabolic disorders, including without limitation diabetes, thyroid gland activity increase;
— endocrine profile changes in the period of sexual maturation (in girls, more often);
— congenital and acquired dysimmunities;
—allergy, including also medicinal and postvaccinal ones;
— rheumatic disorders;
— anaemia;
— severe vitamin deficiencies of vitamins C and B group;
— tumors;
— angioneurosis;
— brain injuries;
— brain diseases (arachnoidite, hypothalamus insufficiency);
— major hemorrhages (hematomas) after injuries;
—physical and mental strain, including the evening motive raise of temperature;
— hyperthermia [9].

At the first stage of investigation of pyrexia reasons, the presence of viral, bacterial, phthisic or other infection shall be excluded. For this purpose, examinations of blood, gag, nose mucus, intestinal contents, urea, USI, radiological investigations are conducted. To date, owing to implementation of enzyme-immunoassay and polymerase chain reaction methods, it is possible to identify much more exactly a specific microorganism — an originator of subfebrility or antibody to it.

Rapid development of virology, implementation of new laboratory diagnostics methods — enzyme- immunoassay (EIA), polymerase chain reaction (PCR) resulted in a significant of advance of our knowledge about causative agents of infections, namely, herpesviruses, and on their role in the emergence of various diseases. If earlier this pathology was studied only by infectiologists, then at now the problem of herpesviral infections is at the intersection of many medical professions — infectology, hematology, oncology, pediatrics, therapy. Manifestations of herpesviral infections are many-faced. There are a great number of diseases associated thereto. The consequences of presence of herpesviruses in the body are numerous. This is exactly why it is so essential to know about virus load as early as possible and prevent possibility of the problem emergence in the future.

Herpetic viruses are widespread enough. According to various authors, up to 90% of adult population worldwide is infected with them. Following data of numerous studies, Epstein-Barr virus is the commonest of herpesviruses group [1, 10, 16, 18]. Most people get infected as early as in childhood and by the age of three years up to 20-70% become its circulators. Additionally, it was identified that the age of contamination depends on social-economic conditions, density of population — in developed countries it is higher than in developing [18].

The infection sources are persons with acute and chronic forms of infection, who emit virus into ambient environment with saliva, nasopharynx mucus. Contamination can be of several types: airborne, sexual, by blood transfusion, possibly, at close and physical contacts, for example, when kissing, using common dishes, linen, hygienic items, toys [10]. In addition, virus may be transferred from mother to fetus — intrauterine infection with congenital abnormalities development. Most people become infected as early as in a childhood, frequently not demonstrating any signs of disease.

Herpesviruses family *(Herpesviridae)* includes 8 classifiable types of human viruses: herpes simplex viruses — herpes simplex virus (HSV-1) and herpes genitalis (HG-2), varicella zoster virus, Epstein-Barr virus, cytomegalovirus, herpes virus of types 6, 7, 8, as well as near 80 non-classifiable human and animals' herpes viruses.

To date, *Herpesviridae* family includes 3 subfamilies: *Alphaherpesvirinae, Bethaherpesvirinae, Gammaherpesvirinae.*

Alphaherpesvirinae subfamily viruses are characterized by a short reproduction cycle with cytopathic effect in the cells of infected cultures. They include herpes simplex virus of type 1 (HSV-I), herpes simplex virus of type 2 (HSV-II), herpes virus of type 3 —varicella zoster virus.

Bethaherpesuvirinae subfamily viruses are characterized by a strictly pronounced pathogenicity for one type of hosts. They include cytomegaloviruses (herpes virus of type 5, CMV).

Characteristics of human herpesviruses and main forms of infection *Table 1*

Herpesviruses	Diseases associated with primary infection	Diseases emerging at activation of latent infection
Herpes simples virus of type 1 (HSV-1)	Primary herpes with preferential injuries of skin face, vermillion borders, oral mucosa, upper extremities skin, meningoencephalitis, neonatal herpes, congenital herpes	Relapsing skin herpes, upper extremities herpes, ophthalmic herpes, relapsing meningoencephalitis
Herpes simples virus of type 2 (HSV-2)	Primary herpes with preferential injuries of genitalis skin and mucosa, buttocks skin, lower extremities skin, meningoencephalitis	Relapsing genitalis, buttocks, thighs herpes, myelitis, encephalitis
Herpes zoster virus (Varicella zoster (HZV, VZV)	Varicella	Herpes zoster, herpes zoster in patients with immunodeficiency
Epstein-Barr virus, type 4 1 EBV)	Infectious mononucleosis, B-lymphoproliferative diseases	Burkitt's lymphoma, nasopharyngeal carcinoma, hairy leukoplakia
Cytomegalovirus, type 5 (CMV)	Primary CMV-infection, congenital CMV-infection	Chronic CMV-infection in immunocompetent persons; acute CV-infection in immunodeficient persons; retinitis, pneumonia, hepatitis, colitis, encephalitis, at transplantation and AIDS
Human herpes virus of type 6 (HHV-6)	Newborns' exanthema	Systemic disease at transplantation
Human herpes virus of type 7 (HHV-7)	Newborns' exanthema	Chronic fatigue syndrome
Human herpes virus of type 8 (HHV-8)	Unknown	Kaposi sarcoma in HIV-seronegative people; Kaposi sarcoma associated with HIV-infection and AIDS

Gammaherpesvirinae family viruses are characterized by strictly pronounced tropisms to B- or T-lymphocytes, in which they are long-term persisting. Among these are: herpes virus of type 4 (Epstein-Barr virus, EBV). herpes virus of type 6 (HHV-6), herpes virus of type 7 (HHV-7), herpes virus of type 8 (HHV-8).

Herpesviridae family herpesviruses refer to DNA-containing viruses, which are persisting in host's body for the term of life. All herpesviruses have a cycle of intracellular parasitizing in nucleus and cytoplasm of an affected cell; in addition, viral particles inclusions are accumulating in a nucleus increasing the sizes both of the nucleus itself and the cell in whole (giant cells pathogenesis). For the purpose of masking against immunocompetent cells of the macroorganism, microorganisms use a membranous mimicry, i.e. form a supplement virions layer of membranous elements of the used cell.

Herpesviruses do not always destroy affected cells. Lifelong infection phenomenon, which is typical for them, consists in persistency of certain tissues in cells with periodical activation.

For example, herpes viruses of types 1 and 2 persist in the cells of paravertebral sensory ganglions of a nervous system, where they are in integrated (genome-built) or free non-reproductive condition. As affected by "trigger", virus gets activated and migrates from ganglion along a peripheral nerve's axon to epithelial cells, where it replicates.

In body, cytomegaloviruses persist in saliva glands. During exacerbation, viruses are detected in blood (viremia) — this is a hematogenic route of infection in a body.

EBV possesses certain affinity, selectivity of interaction with cells, which stipulates contamination on certain types of cells only. The main cell-targets for EBV are B-lymphocytes; however, it may affect epithelium of oral pharynx, salivary ducts, cervix uteri, gastrointestinal tract, vascular endothelium and immunocompetent cells — T-lymphocytes (CD3), natural killer cells (NK-cells CD16), neutrophils, macrophages. B-lymphocytes possess specific receptors for EBV — CD21. Infected B-cells acquire ability to unrestricted proliferation (immortalization, "cellular immortality") and synthesize a great number of heterophil antibodies (polyclonal activation). As all herpesviruses, EBV has a powerful immunosuppressive effect [1,11], results in disorders of an immune response by cellular and humoral types, cytokine status, innate resistance factors, EBV has an ability to lifelong persistence in human body, which is associated with evocation of immunodeficient disease and integration of DNA-virus into cells genome [10,14]. Specific antigens are shown up in lipopolysaccharidic capsid: capsidic (EBV-VCA), nucleus (EBV-EBNA), early (EBV-EA) and membranous.

The properties of virus differ from other herpesviruses known with their "intracellular" aggressiveness. The causative agents of cytomegaly, herpes zoster, genital and labial herpes nearly always destroy cells, which they invade in. EBV behaves more "delicately": it parasitizes in immune cells (B-lymphocytes), enabling them to perform designated functions, and not frequently demonstrates pronounced cytopathic effect towards them [1]. However, it only intensifies a suspicion towards it since such a property of virus, in certain scenarios, may evoke non-controlled degenerative changes in a contaminated body, stipulating the advance of its functions' insufficiency. Accordingly, EBV causes such various diseases as infectious mononucleosis, malignant tumors, autoimmune diseases, secondary immunodeficiency [3-5].

Primary EBV-infection proceeds, as a rule, symptom-free and only in some cases manifests itself as infectious mononucleosis with the development of fever, hepatosplenomegaly, lymphoadenopathy and increasing

Table 2

Fundamental principles of treating children with herpesviral infections

Course		*Specific immunoglobulins*	*Acyclic nucleosides*	*Interferons*	*Immunomodulatory agents (in case of immune disorders)*
Acute clinically significant infections (hepatitis, encephalitis, carditis, anemia, pneumonia)		+	+	+	+
Chronic (relapse) clinically significant		-	+	+	+
Chronic(remission)	*Intercurrent disease, exacerbation of chronic concomitant, FICh (frequently-*	-	-	+	+
	Without comorbidity	-	-	-	-
Latent		-	-	-	-

number of CD8+-T-lymphocytes in peripheral blood [12). These clinical manifestations are stipulated by immune response of T-cytotoxic lymphocytes [17] to polyclonal activation B-lymphocytes typical for EBV-infection. However, after contamination, notwithstanding manifestations of an acute period, virus persistency in B-memory cells is observed throughout life [15]. In this case, number of B-lymphocytes carrying viral DNA is permanent in healthy people and makes nearly 1 per 105- 106 [13].

Domestic and foreign authors investigated that clinical picture of chronic infection evoked by EBV is characterized in adults by long-term syndromes of intoxication, lymphoadenopathy, hepatosplenomegaly, tonsillitis, adenoiditis, in some patients — interstitial pneumonia, uveitis, hepatitis CNS pathologies [4,7,19].

Clinical manifestations of infecting with herpesviruses are many-sided and depend on the type of herpesviruses (Table 1) [8].

Study materials and methods

We analyzed the results of clinical and laboratory examinations of 130 children. The criteria of selection of children for the study were a long-term subfebrility, ARVI incidence more than 4 days per year, ARVI duration over 10 days with complications and over 7 days without complications, lack of genetic, hereditary diseases congenital respiratory defects, parents consent. In order to diagnose contamination with cytomegaloviruses, herpes simples viruses of types I and II, enzyme immunoassay (EIA) method was used, which included identification of specific M and G classes immunoglobulins (IgM and IgG) in blood serum. DNAs of infectious agents were examined by polymerase chain reaction method (PCR). Specific antibodies to EBV were identified — IgM and IgG to early antigen (EA), to capsid antigen (VGA) and nucleus antigen (EBNA) by EIA method in blood serum using diagnostic immunoenzymometric system "Vector-Best" (Russia). Specific IgM appears in an acute phase of disease or in the period of exacerbation and disappears in 4-6 weeks, generally. IgG to EA — antibodies to early antigen (early) appear in an acute phase too, represent markers of active replication and at recovery decrease in 3-6 months. IgG to VGA — antibodies to capsid antigen (early) are identified in an acute period with a maximum by week 2-4, afterwards their number decreases, and threshold level is preserved for a long time. IgG to EBNA — antibodies to nuclear antigen appear in 2-4 months after acute phase, and their production preserves life-long. Cellular and humoral immunity parameters

were identified by the method of immunophenotyping of peripheral blood lymphocytes differentiation clusters: CD-3 (total T-lymphocytes), CD-4 (T-helpers), CD-8 (T-suppressors), CD-16 (NK-cells), CD-20 (B-lymphocytes). Level of cytokines — IL-2, IL-6, IL-8, tumor necrosis factor (TNF) was identified by means of monoclonal antibodies by the method of flow cytofluorometry. The state of phagocytic system was evaluated according to phagocytosis response with identification of phagocytic number, phagocytosis percent and completeness. Circulating immune complexes (CIC) were determined by means of polyethylene glycol-6000. The study of infected children's profiles was conducted under clinical remission. The immune parameters of children under observation were compared with those of 15 apparently healthy peers. Statistical processing was carried out with the use of dialogue statistical system STADIA.

Study results and discussions

Children under observation were reported with a high rate of relapsing respiratory diseases and contamination of otolaryngology system organs with viral infections. During observation all children underwent ARVIs (from 6 to 8 times a year). According to the nature of ARVI clinical manifestations — with complicated course, intoxicating, lymphoproliferative and nasopharyngeal syndromes.

Herpesviral infections were identified in 78 children: cytomegaloviral infections (CMVI) — in 36 (46.2%) children; infections evoked by herpes simplex virus of type I (HSV), — 9(11.5%), Epstein-Barr virus (EBV) - 13 (16.7%); CMVI and EBV associations - 11 children (14.1%); CMVI and HSV associations - 5 (6.4%), HSV and EBV associations - 1 (1.2%), CMVI, EBV and HSV associations - 3 (3.9%). Among them in 17 (21.8%) patients acute infection course was diagnosed (group 1), in 61 (78.2%) – chronic course (group 2).

In children under observation a high rate of relapsing viral respiratory diseases was identified. During observation all children underwent ARVIs (7.4 0.62 per year), which were protracted and complicated. Disease duration made 12.6±0.27 days. In most cases, we registered injuries of respiratory organs; obstructive bronchitis took place in 60 (76.9%) children, pneumonia — in 31 (39.7%).

When studying antenatal anamnesis, it was detected that all children under observation had a high risk of intrauterine infecting. Complicated pregnancy and deliveries were found in 32 cases (41.0%). According to fetal age, 52 (66.7%) children were born mature, antenatal hypotrophy was observed in a half of them, 26 (33.3%) children were born prematurely.

In children with acute course of infection, induced by herpesviruses, the initial signs of disease were characterized by adynamia, body weight increment arrest, temperature rise, predominantly up to subfebrile figures, upper airways inflammations, and in more than 75% of cases broncho-obstructive syndrome was found. When studying peripheral blood, anaemia, neutropenia, relative lymphocytosis, monocytosis was identified.

In children with chronic herpesviral infection course, variability of clinical manifestations was identified. We diagnosed hypotrophy of various degrees (38.5%) and nervous and physical development arrests by 1.5—2 epicrisis terms (44.9%). According to ultrasound and roentgen examinations, hyperplasia of thymus gland was detected in 34.6% children, lymphoadenopathy in 74.4% cases, protracted hepato-splenic syndrome - in 14.1% cases. One third of children were reported having atopic dermatitis manifestations. Against the background of acute ARVI manifestations, the development of broncho-obstructive syndrome was detected in 60 (76.9%) children with predominantly relapsing course.

At immunological investigations of frequently ill children (FICh) infected with herpesviruses, we registered changes in both specific and non-specific components of immune system. For example, when studying humoral immune parameters in children with acute herpesviral infections against the background of a decrease of B-lymphocytes number, the average lg A, M, *G* parameters almost twofold exceeded the age norms. In the second group, in children with chronic course of herpesviral infections, total number of B-cells was somewhat higher. Hyperproduction of immunoglobulins in children with HVI was deemed as reaction to longstanding viral sensitization, which stipulated chronization of an inflammatory process.

The state of T-cellular immune component in children with acute herpesviral infection course was characterized with a significant disbalance. Total T-lymphocytes count and subpopulations thereof exceeded age norms, while production of natural killer cells reduced twofold. CD4/CD8 ratio index was decreased and made 1.29±0.06 in the first group of observed patients at 1.75±0.03 in healthy children ($p<0.05$). At chronic course of herpesviral infection, the state of T-system was more balanced, however, number of killers was reduced, although uncertainly. Notwithstanding activity of immune cellular component in children infected with herpesviruses, the decrease of marker of activation, proliferation and differentiation of T-lymphocytes — IL-2 was found, which was far more apparent at the chronic infection course.

During evaluation of the functional state of neutrophils phagocytic system, it was detected that phagocytising cells percent in both groups of infected children was significantly lower than in healthy peers. Alongside with that, under chronic course, activity and absorption ability of granulocytes far exceeded parameters of children with an acute course. Disbalance with regard to phagocytising cells and phagocytic number percent ratio speaks for phagocytic system strain under still sufficient compensatory abilities of these functions of neutrophils. Digesting properties of phagocytising cells were decreasing in both groups of children notwithstanding the stage of infectious process. For example, children from the first group were found with phagocytosis completeness parameter 0.64± 0.036, children with HVI chronic course — 0.58±0.021, which was significantly lower than in healthy peers. Phagocytosis incompleteness, reduction of phagocytising cells number in children under observation confirms the suggestions concerning participation of herpesviruses in neutrophilic leucocytes apoptosis.

Our attention was called by disbalance of synthesis of pro-inflammatory cytokines, in particular, IL-6, IL-8 FIO of the principal regulating factors of specific reactions of cellular immune component. The obtained results evidence on the predominant influence of pro-inflammatory cytokines in FICh infected with herpesviruses. For example, it was established that most children of the first group (75.6%) had materially high levels of the observed cytokines. At the chronic course of infectious process, production of interleukins was increased by 1.5-2.0 times versus parameters in children of the first and control groups.

The particularly high and statistically significant parameter of immune system functions incoordination appeared to be a repeated increase of CIC level. For example, in the first group, CIC concentration made 187.6+59.65 absorbance units (at 55.2+4.28 age norm). Children with chronic infection course had somewhat lower CIC level, although materially exceeding normal parameters too (126.8+22.14). It was deemed to be an advance of pathological process owing to sedimentation of immune complexes on certain tissues. The development of such inflammatory reaction in FICh infected with herpesviruses, apparently, stipulates formation of the subsequent cases of chronic diseases, including autoimmune and allergic ones.

Consequently, in the early period of contamination in infants against the background of a high antigen load, the immune adaptation system gets activated manifesting in the increase of pro-inflammatory cytokines concentrations. A longstanding persistency of herpesviruses in a child's body results in immune breakdown: a pronounced synthesis of pro-inflammatory cytokines, which play a key role in chronic systemic inflammation development. In this regard, it is necessary that a complex of treatment and rehabilitation measures for FICh, particularly those infected with herpesviruses, should include not only correction of the immune states of ill children, but also take into account a balance of pro- and anti-inflammatory cytokines production.

It should be emphasized that none of currently known antiviral and other drugs can completely eliminate herpesviral infection from a body. In many respects, it is conditioned by predominance of intracellular existence, impossibility of adequate enough penetration of chemotherapeutic agents into a cell and difficulty of its neutralization and removal, accordingly. Therefore, herpesviral infection management tactics is largely determined by the incidence, exacerbations severity level, diseases complications, and by infection transfer risk, as well. And the task of therapeutic measure consists in prevention and treatment of infectious process exacerbations and complications development (Table 2).

Method of treatment of children with active infections caused by herpesviruses consists in that children with identified active HVI course (acute or exacerbated chronic) with the pronounced clinical manifestations and injuries of organs should use combinations of acyclic nucleosides

(Acyclovir, Valtrex), recombinant α-interferon, enabling improvement of state of immunological reactivity of a body and having no influence on the level of interferons participating in autoimmune processes development at the same time.

For the purpose of longstanding viral suppression, herbal drug "Flavozid" having been developed in Ukraine is used, which possesses a pronounced antiviral activity (virus replication blocking), ability to induce endogenic interferons (α and γ), stimulating effect on tissular macrophages' functions and antioxidant properties.

Methodology of using Flavozid in comprehensive treatment of herpesviral infection in infants — 0.5 ml 2 times a day, 2-4 weeks, children in 1-2 years age — 1 ml 2 times a day, 2-4 weeks, children in 2-4 years age — 1.5 ml 2 times a day from the first to third day, 3 ml 2 times a day from the 4th day, children in 4-6 years age — 3 ml 2 times a day from the first to third day, 4 ml 2 times a day from the 4th day, children in 6-9 years age - 4 ml 2 times a day from the first to third day, 5 ml 2 times a day from the 4th day, children in 9-12 years age - 5 ml 2 times a day from the first to third day, 6 ml 2 times a day from the 4th day. Duration of treatment — 1 month

At relapsing course of infection, treatment courses with Flavozid should be carried out 3-4 times a year, at latent — twice a year.

Conclusions

Against the treatment conducted, we managed to stabilize acute infection signs in 67.9% of children, shift relapsing courser of chronic herpesviral infection to a latent one — in 65.4%. After treatment in 66 (84.6%) cases, subfebrility disappearance and improvement of patients' overall health was observed. 59 (75.6%) children were reported with decreasing lymph glands. Number and duration of recurrent respiratory diseases and incidence of complications, as well, was reduced by 2.5 times.

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