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INFECTIOUS MONONUCLEOSIS IN CHILDREN AND WAYS OF IMPROVEMENT THE TREATMENT OF PATIENTS

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The beginning of this century is characterized by an epidemic of herpesvirus infections, whose frequency and spread continue to rise. Infection by the herpes virus group occurs mainly during the first five years of life and leads to life-long persistence [1,2]. The most common disease among children, which can be caused by viruses mentioned above, is mononucleosis-like syndrome. The development of this syndrome is associated with many factors, however, main causes are b- and g-herpes viruses.

Despite the similarity of clinical features of the syndrome of infectious mononucleosis (IM) caused by cytomegalovirus, human herpes virus type 6 and Epstein-Barr virus (EBV), pathogenic differences occurring in the body should be realized. Thus, b-herpes virus (cytomegalovirus, human herpes virus type 6) is characterized by a primary lesion of T-cell-level immune system, while g-herpes virus (EBV) have lymfotrophy and is capable to replicate in B-lymphocytes, which it penetrate in via receptor CR2 (CD 21) [2,3]. It is known that the development of different variants of clinical course of IM, caused by EBV, is due to an imbalance of cytokine response at the onset of the illness, inability to cellular, humoral immunity and nonspecific resistance factors [4,5]. In addition, it is known that EBV protein expressed by BCRF-1 coincides with the cytokine IL-10 in amino acids' sequence, and cause its mimicry. Thereby it contributes to suppression of the synthesis of IFN-γ by peripheral mononuclear cells. Other BARF-1 protein performs functions as a soluble receptor for IL-1, and blocks the activity of IFN-γ. This provides a "slipping" of the virus from immune surveillance during acute infection and during its reactivation. Thus, EBV infection is considered the disease of the immune system in violation of the development of interferon, and the immunosuppressive effect of the virus leads to activation of secondary flora, engaging in the various organs [5,6]. At the same time, the defeat of immune by viruses supports and enhances transient immune deficiency, leads to activation of secondary flora and to sensitization of the body by viral antigens. Despite the presence of specific antiviral drugs up to the date, scientists haven't managed to reduce pathogen circulation in the human population and to achieve absolute elimination of the virus from the body of an infected person. The lack of specific measures for the prevention of disease is the main cause. Surprisingly, the use of acyclovir group drugs are not prescribed according to current treatment protocols, even in severe forms of the disease [7]. Questions about the use of nonspecific antiviral and «immunomodulatory» drugs against herpes virus infections get a mixed response. The point is that "stimulation" of immune cells in the background of immunosuppression, which is typical for most viruses, can be extremely dangerous. Therefore, in the treatment of children suffering from IM is important to select drugs that are not harmful to the body, have antiviral effect, and at the same time, normalize work of immune cells. Interferons are drugs, which have all the necessary properties. They are natural factors of nonspecific defence produced by a human organism during the invasion into the body of any infectious pathogen. These specific proteins were discovered in 1957 by chance during experiments employees of the London National Institute virologists Englishman A. Isaacs and Swiss J. Lindemann. Interferons activate the immune response and the cells become refractory against the virus. Interferons in the body increase the activity of T-helper cells, cytotoxic T-lymphocytes, enhance the phagocytic activity and the intensity of the differentiation of B-lymphocytes. Interferons do not have specificity, thus, are effective against different viruses [8]. The last fact is extremely important according to the pathoetiology IM. It was proved, that interferons increase the effectivity of immune response against viruses in cells, which were transformed into cancer cells. It is well known, that EBV refers to viruses that can cause uncontrolled replication of lymphoid and reticular tissue. EBV belongs to oncogenic viruses, and is regarded as the cause of Lymphoma Berketa, Nasopharyngeal Carcinoma, B-cell tumours in immunocompromised people [5,9]. The use of interferon in the treatment for IM is expedient in terms of reducing the risk of side effects of drugs, especially - derivatives of acyclovir, using of which can lead to a number of adverse events from the cardiovascular, nervous and hematopoietic systems, gastrointestinal tract, and so on.

At the same time, not only adults but children can use interferon drugs, including infants and pregnant women. Considering all the above, the question of improving the treatment of patients with IM remains a pressing issue of infectology.

The purpose of the study - to examine the efficacy of interferon in the treatment of children with IM.

Materials and methods

At the Regional Children's Hospital of Infectious Diseases, Kharkiv the comparison of the dynamics of clinical and laboratory parameters of 102 children in the age 1-5 years with moderate tonsillar-glandular form of IM was conducted. The control group consisted of 58 children whose treatment was performed in accordance with generally accepted schemes of existing protocols for diagnosis and treatment of infectious diseases in children [7] The main group contained 44 patients, which had a complex therapy with the combination of recombinant interferon alpha-2 Viferon-Fearon at doses of 500 000 IU, 2 times a day during 5 days. Our choice of this particular drug was due to the form of drug release - suppositories, the use of which increases the absorption rate of the active substance and reduces the load on the mucous membrane of the stomach and intestines. In addition, the product contains ascorbic acid and tocopherol acetate, which are powerful antioxidants and membrane-stabilizing factors.

Children in both groups were comparable in age (18,64 ± 2,73 and 20,22 ± 2,56 months respectively in groups, $p>0,05$) and premorbid background. The disease was caused by Epstein-Barr virus, which was determined by the standard immuno-enzyme test (the presence of IgM

antibodies to earlier and/or the capsid antigen) and by PCR (nucleic acid of EBV).

Results and discussion

The classic signs of IM were found in the majority of children in the debut of the disease. The disease started acutely with fever, symptoms of intoxication, tonsillitis (lacunar tonsillitis), and the increase in size of submandibular and cervical lymph nodes, difficulty in nasal breathing. All the children in the hospital had swelling of face and hepatomegaly, which diagnostic value in infants is not so important, because the increase of liver relative to the size of the chest is physiological. At the same time, 22 (21,6%) children had slow onset, which was characterized by catarrhal symptoms and gradual rise in temperature. Serous discharges from the nose, nasal congestion, dry cough that gradually became moist, appearance of "snoring" during sleep were the main catarral symptoms. An acute respiratory disease was diagnosed for children at the first visit to the pediatrician, and symptomatic therapy was used during three to five days as a primary treatment. However, the fever persisted, catarrhal manifestations and signs of intoxication intensified - rejection of food appeared, the child was becoming lethargic, and parents started to pay attention on the neck lumps of. Prolonged fever and swollen lymph nodes were a major cause of hospitalization. Clinical examination of children, who proceeded to the hospital, had revealed the symptoms of tonsillitis. But membranes on the tonsils were found only in 10 patients; the other patients had hyperaemia or "looseness" of the oropharynx mucosa.

The ultrasound of the abdomen was conducted for all patients during the hospital stay, which showed an increase in the size of the liver, signs of parenchymal reaction of liver. At the same time, increasing the size of the spleen was observed in 67 patients (65,7%), and in 36 patients (35,3%) signs of hepatosplenitis were found. An increase in aminotransferase levels was found in biochemical analysis of liver samples in 21 children (20,6%), but these figures decreased to physiological norms at the time of discharge from the hospital. Despite the known contraindications on the use of Ampicillin in the treatment for IM, this drug was prescribed for 11 patients (10,8%) in the outpatient basis, which led to appearance of immunocomplex rash with the hemorrhagic component in 2 (1,9%) of them.

In peripheral blood leucocytosis ($15,48\pm2,78*10^9$ /L) and lymphocytosis (72,66±3,58%), monocytosis (13,06±2,31%), accelerated ESR (18,96±3,22 mm/h) were found. Only 57 children (55,9%) had abnormal blood mononuclear cells (virocytes), whose number was not high and reached 6,84±1,67%. Patients had thrombocytopenia to $155,49 \pm 13,22*10^9$ /L in 15 cases (14,7%) and anaemia in 19 (18,6%) patients.

We analyzed the efficiency of the use of the recombinant interferon in complex treatment, based on a comparative analysis of the dynamics of basic clinical and laboratory parameters of the two groups of patients. Results are compared in the table.

Table. Duration of main clinical and laboratory characteristics of patients, (M ± m, days)

Sign	The main group (n=44)	Control group (n=58)
Fever	5,18±1,12	7,96±0,77*
Intoxication	3,52±1,25	4,25±1,07
Decrease of the appetite	3,11±0,84	4,05±1,24
Nasal congestion	4,06±0,98	6,68±0,82*
Tonsillitis	3,24±1,26	4,88±1,08
Lymphadenopathy	4,98±1,11	7,95±0,87*
Hepatomegaly	7,65±1,16	10,98±1,15*
Splenomegaly	6,08±1,07	7,41±1,59
Leucocytosis	7,01±2,08	9,64±1,87
Accelerated ESR	7,19±1,06	10,42±1,17*
Length of hospital stays	9,02±1,21	12,84±1,43*

*Note. * - probability of signs, p<0,05.*

As the table shows, accelerated regression of clinical symptoms and laboratory parameters was found in children, to whom complex therapy with recombinant interferon alpha 2 (Viferon-Fearon) was used. Significant differences in clinical parameters were found in terms of normalization of body temperature (5,18 ± 1,12 vs 7,96 ± 0,77 days, p<0,05), elimination of nasal breathing difficulty (4,06 ± 0,98 vs 6 68 ± 0,82, p<0,05), reducing the size of the regional lymph nodes (4,98 ± 1,11 vs 7,95 ± 0,87, p<0,05) and liver (7,65 ± 1, 16 vs 10,98 ± 1,15 days, p<0,05). The positive effect of interferon on peripheral blood caused an early normalization of leukocytes and ESR, the last one occurred significantly faster (7,19 ± 1,06 vs 10,42 ± 1,17 days, p<0,05). The duration of treatment of the main group in hospital was 9,02 ± 1,21 days while the treatment of the control group lasted 12,84 ± 1,43 days, p<0,05. Prescription of Viferon made it possible to shorten the hospital stays of patients in approximately 3-4 days.

Thus, one of the most perspective ways to improve the treatment for EBV IM in children is the use of recombinant interferon alpha-2. In addition to positive effects on the clinical course of the disease, the advisability of appointing this drug is due to its probability of development IM in young children alike to respiratory infections. Prescribing Viferon in first hours of the appearing of catarrhal symptoms in children is appropriate, regardless of the results of further definition of the ethology of the disease, because there are many studies that prove the efficacy of interferon for acute respiratory viral infections in children also [10,11].

Conclusions

1. Early clinical diagnosis of IM caused by EBV in young children has difficulties because of possible "atypical» onset of the disease similar to acute respiratory illness.
2. Virocytes couldn't be found in peripheral blood of almost half of young children, suffering from IM, but lymphocytosis and monocytosis are typical. Thus, the final diagnostic tests for those children are ELISA and PCR studies.
3. The use in the treatment for children with EBV IM recombinant interferon alpha-2 (Viferon-Fearon) promotes regression of clinical symptoms and accelerates the normalization of laboratory values, reduces the duration of hospital stays of patients.

References

1. Lezhenko G.O. Infectious mononucleosis in children: clinical and immunological characteristics [Text] / G.O. Lezhenko, O.V. Usachova, Ye.A. Silina, T.M. Pakholchuk //. – Current infectology 2013. – N1 (1). – P. 56-60.
2. Tyunyaeva N.O. Infectious mononucleosis: etiological factors, diagnosis and treatment problems [Text] / N.O. Tyunyaeva, L.V. Sofronova // Journal of New Medical Technologies. – 2014. – V. 21, № 3. – P. 184-190.
3. Jenson H.B. Epstein-Barr virus [Text] / H.B. Jenson //Pediatr Rev. – 2011. – V. 32(9). – P. 375-83.
4. Chijioke O, Azzi T, Nadal D, Münz C. Innate immune responses against Epstein Barr virus infection. [Text] / J Leukoc Biol. 2013;94(6):1185-90.
5. Kelly G.L. An Epstein-Barr virus anti-apoptotic protein constitutively expressed in Burkett lymphomagenesis. [Text] / G.L. Kelly, H.M. Long, J. Stylionou, W.A. Thomas et al. // PLoS Pathog., 2009, 5(3), p.1000341.
6. Paschos K. Epstein-Barr virus latency in B-cells leads to epigenetic repression and CpG methylation of the tumour suppressor gene Bim. PLoS. [Text] / K. Paschos, P. Smith, E. Anderton et al. // Pathog., 2009, 5(6), p. 1000492.
7. Order № 354, 09.07.2004 «On approval of protocols for diagnosis and treatment of infectious diseases in children» [E-version]. http://mozdocs.kiev.ua/view.php?id=3292
8. Shtro A.A. Interferon activity in combination with antioxidants against DNA and RNA-containing Human viruses [Text] / A.A. Shtro, A.V. Slita, L.A. Carpinskaya et al. //. – 2012. Attending doctor – N 10. – P. 22–26. ISSN 1560-5175.
9. Baricheva L.Y. Factors and mechanisms of immunosuppression with Epstein-Barr virus infection [Text] / L.Y.Baricheva, M.V. Golubeva, A.V. Volkova // Childhood Infections. – 2014. – V.13, N2. – P. 28-33. ISSN 2072-8107.
10. Gorelov A. V. Interferon preparations in therapy of acute respiratory viral infections and flu in newborns and infants/ A. V. Gorelov, I. L. Alimova, T. I. Antonova, L. V. Feklisova et al. [Text] // Attending doctor. – 2015. - №1. – P. 7-14 ISSN 1560-5175.
11. Yulish Ye.I. Etiopathogenetic therapy of acute respiratory Viral infections in children [Text] / Ye.I. Yulish, O.Ye. Chernyshova // Child`s Health. – 2014. – N1(52). – P.129-133. ISSN 2224-0551.

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Materials and methods. At the Regional Children's Hospital of Infectious Diseases, Kharkiv the comparison of the dynamics of clinical and laboratory parameters of 102 children in the age 1-5 years with moderate tonsillar-glandular form of IM was conducted. The diseases were caused by EBV. The control group consisted of 58 children whose treatment was performed in accordance with generally accepted schemes of existing protocols for diagnosis and treatment of infectious diseases in children. The main group contained 44 patients, which had a complex therapy with the combination of recombinant interferon alpha-2 Viferon-Fearon at doses of 500 000 IU, 2 times a day during 5 days. Our choice of this particular drug was due to the form of drug release - suppositories. In addition, the product contains ascorbic acid and tocopherol acetate, which are powerful antioxidants and membrane-stabilizing factors.

Results and discussion. In the majority of children the disease started acutely with fever, symptoms of intoxication, tonsillitis (lacunar tonsillitis), and the increase in size of submandibular and cervical lymph nodes, difficulty in nasal breathing. At the same time, 22 (21,6%) children had slow onset, which was characterized by catarrhal symptoms and gradual rise in temperature. Serous discharges from the nose, nasal congestion, dry cough that gradually became moist, appearance of "snoring" during sleep were the main catarral symptoms. An acute respiratory disease was diagnosed for children at the first visit to the pediatrician, and symptomatic therapy was used during three to five days as a primary treatment. However, the fever persisted, catarrhal manifestations and signs of intoxication intensified, and parents started to pay attention on the neck lumps of. Prolonged fever and swollen lymph nodes were a major cause of hospitalization. Clinical examination of children, who proceeded to the hospital, had revealed the symptoms of tonsillitis. But membranes on the tonsils were found only in 10 patients; the other patients had hyperaemia or "looseness" of the oropharynx mucosa. The ultrasound of the abdomen was conducted for all patients during the hospital stay, which showed an increase

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