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## WAYS TO IMPROVE THE THERAPY OF ESCERICHOSIS IN CHILDREN INFECTED WITH EPSTEIN-BARR VIRUS

Pathogenic escherichia in young children remains one of the main factors of bacterial lesions of the gastrointestinal tract.

**Aim.** To study the effectiveness of the use of interferons in the treatment of escherichiosis in children infected with Epstein-Barr virus (EBV).

**Materials and methods.** At the premises of the Regional Children Infectious Clinical Hospital of Kharkiv a comparison of dynamics of the clinical and laboratory parameters of 68 children aged 1-3 years old with a moderate form of escherichiosis and infected with EBV (inactive persistent form) was performed. The first group consisted of 47 children whose treatment was carried out according to the generally accepted schemes; the second group was 21 children receiving recombinant interferon alfa-2 in the complex therapy in the age-related doses twice a day for 5 days.

**Results.** Significant difference within the time of fever preservation ( $4.73 \pm 0.37$  versus  $3.25 \pm 0.21$  days,  $p < 0.01$ ) and disappearance of the general intoxication symptoms ( $4.02 \pm 0.29$  vs.  $2.24 \pm 0.35$ ,  $p < 0.01$ ) were determined. According to the ultrasound study normalization of defecation ( $5.91 \pm 0.22$  vs.  $4.34 \pm 0.29$  days,  $p < 0.01$ ) and elimination of signs of the parenchymal liver reaction ( $5.94 \pm 0.39$  vs.  $4.15 \pm 0.50$  days,  $p < 0.05$ ), as well as mezadenite phenomena ( $8.67 \pm 0.86$  vs.  $6.19 \pm 0.77$  days, respectively,  $p < 0.05$ ) were statistically significant in children of the first group. The positive effect of interferon therapy on the parameters of the clinical blood analysis was manifested in the faster normalization of the amount of leukocytes and ESR ( $7.55 \pm 0.61$  vs.  $5.44 \pm 0.48$  days,  $p < 0.05$ ). In general, duration of patient's staying at hospital in children of the first group was  $10.64 \pm 0.53$  days, while in the second group it was  $8.09 \pm 0.36$  days,  $p < 0.01$ .

**Conclusions.** The use of recombinant interferon alfa-2 in the complex therapy of escherichiosis in children infected with EBV positively affects the regression of clinical manifestations, accelerates normalization of the laboratory and instrumental indices, and reduces duration of patient's staying at hospital.

**Key words:** escherichiosis; Epstein-Barr virus; children; treatment

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### Шляхи удосконалення терапії дітей, хворих на ешерихіоз, інфікованих вірусом Епштейна-Барра

Патогенні ешерихії у дітей раннього віку залишаються одним із основних чинників бактеріального ураження шлунково-кишкового тракту.

**Мета роботи** – вивчення ефективності застосування інтерферонів у комплексній терапії ешерихіозу у дітей, інфікованих вірусом Епштейна-Барра (ВЕБ).

**Матеріали та методи.** На базі обласної дитячої інфекційної клінічної лікарні м. Харкова проведено співставлення динаміки клініко-лабораторних показників 68 дітей віком від 1 до 3 років, хворих на середньотяжку форму ешерихіозу та інфікованих ВЕБ. Першу групу склали 47 дітей, лікування яких проводили за загальноприйнятими схемами, другу – 21 пацієнт, у комплексній терапії яких використовували рекомбінантний інтерферон альфа-2 у вікових дозах 2 рази на добу впродовж 5 діб.

**Результати.** Визначено вірогідну різницю у строках збереження лихоманки ( $4,73 \pm 0,37$  проти  $3,25 \pm 0,21$  доби,  $p < 0,05$ ) і зникнення симптомів загальної інтоксикації ( $4,02 \pm 0,29$  проти  $2,24 \pm 0,35$  відповідно у групах,  $p < 0,05$ ). У дітей першої групи раніше відбувалась нормалізація випорожнень ( $5,91 \pm 0,22$  проти  $4,34 \pm 0,29$  доби,  $p < 0,05$ ) і зникнення ознак паренхіматозної реакції печінки за даними ультразвукового дослідження ( $5,94 \pm 0,39$  проти  $3,43 \pm 0,30$  діб,  $p < 0,05$ ). Позитивний вплив інтерферонотерапії на показники клінічного аналізу крові виявлявся у швидшій нормалізації кількості лейкоцитів і ШОЕ ( $7,55 \pm 0,61$  проти  $5,44 \pm 0,48$  діб,  $p < 0,05$ ). У цілому строки перебування дітей першої групи у стаціонарі склали  $10,64 \pm 0,53$  доби, в той час як другої –  $8,09 \pm 0,36$  доби,  $p < 0,05$ .

**Висновки.** Застосування в комплексній терапії ешерихіозу у дітей, інфікованих ВЕБ, рекомбінантного інтерферону альфа-2 позитивно впливає на регресію клінічних проявів, прискорює нормалізацію лабораторно-інструментальних показників, скорочує строки перебування хворих у стаціонарі.

**Ключові слова:** ешерихіоз; Епштейна-Барра вірус; діти; лікування

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### **Пути совершенствования терапии детей, больных эшерихиозом, инфицированных вирусом Эпштейна-Барра**

Патогенные эшерихии у детей раннего возраста остаются одним из основных факторов бактериального поражения желудочно-кишечного тракта.

**Цель работы** – изучение эффективности применения интерферонов в комплексной терапии эшерихиоза у детей, инфицированных ВЭБ.

**Материалы и методы.** На базе областной детской инфекционной клинической больницы г. Харькова проведено сопоставление динамики клинико-лабораторных показателей 68 детей 1-3 лет, больных среднетяжелой формой эшерихиоза и инфицированных ВЭБ. Первую группу составили 47 детей, лечение которых проводили по общепринятым схемами, вторую – 21 пациент, в комплексной терапии которых использовали рекомбинантный интерферон альфа-2 в возрастных дозах 2 раза в сутки в течение 5 суток.

**Результаты.** Определена достоверная разница в сроках сохранения лихорадки ( $4,73 \pm 0,37$  против  $3,25 \pm 0,21$  суток,  $p < 0,05$ ) и исчезновение симптомов общей интоксикации ( $4,02 \pm 0,29$  против  $2,24 \pm 0,35$ ,  $p < 0,05$ ). У детей первой группы ранее происходила нормализация стула ( $5,91 \pm 0,22$  против  $4,34 \pm 0,29$ ,  $p < 0,05$ ) и исчезновение признаков паренхиматозной реакции печени по данным ультразвукового исследования ( $5,94 \pm 0,39$  против  $3,43 \pm 0,30$ ,  $p < 0,05$ ). Положительное влияние интерферонотерапии на показатели клинического анализа крови определялось в быстрой нормализации количества лейкоцитов и СОЭ ( $7,55 \pm 0,61$  против  $5,44 \pm 0,48$  суток,  $p < 0,05$ ). Сроки пребывания в стационаре детей первой группы составили  $10,64 \pm 0,53$  суток, в то время как второй –  $8,09 \pm 0,36$  суток,  $p < 0,05$ .

**Выводы.** Применение в комплексной терапии эшерихиоза у детей, инфицированных ВЭБ, рекомбинантного интерферона альфа-2 положительно влияет на регрессию клинических проявлений, ускоряет нормализацию лабораторно-инструментальных показателей, сокращает сроки пребывания больных в стационаре.

**Ключевые слова:** эшерихиоз; Эпштейна-Барра вирус; дети; лечение

Pathogenic escherichia in young children remains one of the main factors of bacterial lesions of the gastrointestinal tract [1, 2]. Taking into account the anatomical and physiological peculiarities of children of the first years of life escherichiosis can cause life-threatening complications for a short period of disease, such as dehydration, acute renal insufficiency, sepsis, etc. [3, 4]. The outbreaks of an infectious disease primarily depend on an adequate immune response of the organism, a balanced response of specific and non-specific defense factors against pathogen invasion [5]. Many factors can affect the functioning of the immune system of the human body, and one of such factors is infection with herpes viruses. Increasingly, doctors of different profiles are faced with a high percentage of children infected with Epstein-Barr virus (EBV), which belongs to the group of herpes viruses, the frequency and prevalence of it among the population continues to grow [6]. Infection with EBV occurs predominantly at an early age and can lead to lifelong persistence [7], therefore, it is not surprising that at the present stage of human development, mixed infections are registered more often [8], even among children. The presence of co-infection in a child leads to certain difficulties in the therapy of the patient, especially when he/she is infected with EBV. The "escape" of the virus from immune surveillance in EBV infection is due to the expression of the BCRF-1 and BARF-1 virus protein, which together result in a decrease in the synthesis of INF- $\gamma$  by peripheral mononuclear cells. Such an immunosuppressive action of VEB promotes the activation of the secondary flora, may affect the

course of the underlying disease [9, 10]. Therefore, in our opinion, the topical issue of pediatric infectious diseases is the search for optimization of the treatment of children with escherichiosis infected with EBV. To date, there are conflicting views on the treatment of EBV infection in children, in existing protocols even with severe forms of the disease there is no information on the use of drugs of the acyclovir group [11]. At the same time, the latter have a large number of side effects and contraindications, and the use of immunomodulators in infectious pathology should be very careful [12, 13]. Unfortunately, no studies on the treatment of escherichiosis in children infected with EBV have been found in the sources available to us.

The **aim** is to study the effectiveness of the use of interferons in the treatment of escherichiosis in children infected with EBV.

### **Materials and methods**

At the premises of the Regional Children Infectious Clinical Hospital of Kharkiv a comparison of dynamics of the clinical and laboratory parameters of 68 children aged 1-3 years old with a moderate form of escherichiosis and infected with EBV (inactive persistent form) was performed. The first group consisted of 47 children whose treatment was carried out according to the generally accepted schemes in accordance with the applicable Protocols for the diagnosis and treatment of infectious diseases in children [11]; the second group was 21 children receiving recombinant interferon alfa-2 in the complex therapy in the age-related doses twice a day for 5 days. The drug in the form of a suppository

Table

**Duration of the main clinical and laboratory parameters, (M ± m, day)**

Symptom	The first group (n=47), M±m	The second group (n=21), M±m
Fever	4.73±0.37	3.25±0.21*
Symptoms of intoxication	4.02±0.29	2.24±0.35*
Decreased appetite	3.77±0.38	3.03±0.28
Vomiting (regurgitation)	3.05±0.25	2.41±0.37
Diarrheal syndrome	5.91±0.22	4.34±0.29*
Flatulence	2.11±0.28	2.34±0.27
Abdominal pain	3.21±0.74	2.18±0.33
Pathological admixtures in feces	4.36±0.38	3.04±0.65
Hepatomegaly	6.28±0.24	3.08±0.61
Parenchymal liver reaction (ultrasound)	5.94±0.39	4.15±0.50*
Signs of mesadenitis (ultrasound)	8.67±0.86	6.19±0.77*
Normalization of the peripheral blood parameters	7.55±0.61	5.44±0.48*
Duration of staying at hospital	10.64±0.53	8.09±0.66*

Note: \* – probability of the sign,  $p < 0.05$ .

promotes the absorption of the active substance, reduces the load on the mucous membrane of the stomach and intestines. The presence of ascorbic acid and tocopherol acetate in the drug increases the anti-inflammatory effect due to the powerful antioxidant and membrane-stabilizing action of the abovementioned components. The formulation of the diagnosis was conducted in accordance with the ICD-10 after the analysis of clinical, bacteriological, virological and serological data of patients. The persistent EBV infection was diagnosed in the presence of high titers of antibodies to anti-IgG capsid antigens (EBV CA) in the patient's disease dynamics. The children of both groups were comparable by age ( $16.56 \pm 2.44$  and  $17.34 \pm 2.27$  months, respectively in groups,  $p < 0.05$ ), gender and pre-morbid background. Statistic processing of the results was carried out using Excel and Statistica 6.0.

### Results and discussion

The analysis of clinical and laboratory data has shown that at the present stage in the Kharkiv region escherichiosis in young children infected with EBV in the overwhelming majority of cases (62-91.18 %) begins abruptly with the body temperature rise (60-88.23 %), disorders of the general condition (54-79.41 %), decreased appetite (57-83.82 %), diarrhea syndrome (59-86.76 %), vomiting or regurgitation (32-47.06 %).

When patients entered the hospital, attention was drawn to hyperemia of the oropharynx (53-77.94 %), an increase in the lymph nodes of the submandibular and cervical group (58-85.29 %), abdominal tenderness during palpation (62-91.18 %), flatulence (28-41.18 %) and the liver enlargement (58-85.29 %). There was a disparity between the frequency of detection of the oropharynx hyperemia (1.66 times

more often) and the parents' complaints of vomiting or catarrhal manifestations that could explain this hyperemia. The sizes of the increased regional lymph nodes varied from 0.5x0.5 cm to 1.5x1.5 cm, were painless when palpated. Intestinal dysfunction was accompanied by liquid feces with mucus admixtures 50-73.53 %) and/or undigested food (59-86.76 %). When studying the parameters of the peripheral blood only 37 (54.41 %) and 30 (44.12 %) patients, respectively, had the changes characteristic for bacterial inflammatory processes in the form of neutrophilia and increased ESR. The additional ultrasound examination of the abdominal cavity organs revealed the parenchymal reaction of the liver in all patients, in 35 patients (51.47 %) – parenchyma echogenicity increased by more than the tenth gradation, in 48 children (70.59 %) there were the signs of mesadenitis. At the same time, according to the biochemical study, only 6 children (8.82 %) showed a moderate elevation of ALAT with normalization of the index to the period of convalescence.

The results of dynamics of the main clinical and laboratory parameters of patients depending on the treatment provided are given in Tab.

The results obtained indicate that in children whose complex therapy involved recombinant interferon alfa-2 a faster regression of clinical symptoms and instrumental indices was observed. Significant difference within the time of fever preservation ( $4.73 \pm 0.37$  versus  $3.25 \pm 0.21$  days,  $p < 0.01$ ) and disappearance of the general intoxication symptoms ( $4.02 \pm 0.29$  vs.  $2.24 \pm 0.35$ ,  $p < 0.01$ ) were determined. According to the ultrasound study normalization of defecation ( $5.91 \pm 0.22$  vs.  $4.34 \pm 0.29$  days,  $p < 0.01$ ) and elimination of signs of the parenchymal liver reaction ( $5.94 \pm 0.39$  vs.  $4.15 \pm 0.50$  days,

$p < 0.05$ ), as well as mezadenite phenomena ( $8.67 \pm 0.86$  vs.  $6.19 \pm 0.77$  days, respectively,  $p < 0.05$ ) were statistically significant in children of the first group. The positive effect of interferon therapy on the parameters of the clinical blood analysis was manifested in the faster normalization of the amount of leukocytes and ESR ( $7.55 \pm 0.61$  vs.  $5.44 \pm 0.48$  days,  $p < 0.05$ ). In general, duration of patient's staying at hospital in children of the first group was  $10.64 \pm 0.53$  days, while in the second group it was  $8.09 \pm 0.36$  days,  $p < 0.01$ .

In our opinion, the positive effect of involving interferon in the complex therapy of children with escherichiosis infected with EBV is due to the ability of interferons to enhance the activity of T-helper cells, cytotoxic T-lymphocytes, increase the phagocytic activity of cells and the intensity of differentiation of B-lymphocytes since interferons are natural factors of non-specific protection during invasion of any infectious pathogen into the body [14].

Thus, the use of recombinant interferon alpha-2 is one of the promising ways to improve the treatment of escherichiosis in young children with latent EBV infection. The early prescription of recombinant interferon alpha-2 in the treatment of

escherichiosis in the presence of catarrhal manifestations in children is especially effective, regardless of the results of further determination of the etiology of the disease since many researchers indicate the effectiveness of interferon use in infections of the various nature [15].

#### CONCLUSIONS

1. Escherichiosis in children infected with VEB is characterized by acute onset of the disease, prolonged fever, dyspeptic symptoms, signs of hyperemia of the oropharynx, enlarged lymph nodes (submandibular; cervical, mesenteric), hepatomegaly with the parenchymal liver reaction, the moderate peripheral blood reaction.

2. The use of recombinant interferon alpha-2 in the complex therapy of escherichiosis in children infected with EBV positively affects the regression of clinical manifestations, accelerates normalization of the laboratory and instrumental indices, and reduces duration of patient's staying at hospital.

3. In our opinion, when detecting EBV infection in children with escherichiosis it is necessary to use preparations of interferons in the complex therapy.

**Conflict of Interests:** authors have no conflict of interests to declare.

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