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VEB-MONONUCLEOSIS IN CHILDREN AT THE HOSPITAL STAGE IN MODERN CONDITIONS

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VEB-mononucleosis is an actual infection of childhood. We analyzed 764 medical records of inpatients with VEB mononucleosis. Two groups of patients were formed: group I (young age) was 411 people (from 1 to 7 years), group II (school age) 353 people (from 7 to 17 years). In the I group, boys predominated, the peak of the disease occurred in the spring period, in group II – girls, the incidence of the incidence was noted in the winter. In both groups, moderate forms of the disease predominated, 684 people (89.5%). Severe forms of the disease prevailed in the children of group II. In group I the disease began acutely, and in the second group – subacute. In both groups, the whole syndrome of VEB mononucleosis was observed: fever, intoxication, acute tonsillitis, lymphadenopathy. The defeat of the nasopharynx and hepatosplenomegaly was more common in the I group. In this case, the increase in the size of the liver and spleen was up to 2 cm from the age norm. In the biochemical analysis of blood, an increase in ALT activity was detected with the same frequency in both age groups. Moreover, in the I group there was a moderate activity of ALT, in the II group – more significant. In clinical blood analysis, most patients in both age groups had leukocytosis. Lymphocytosis was more common in children of group I. Monocytosis was more common in children of group II. Increased ESR was observed in both groups with the same frequency. Atypical mononucleary in children of the I group appeared on the first, and in the older group – on the second week of the disease. A set of laboratory methods was used to diagnose VEB mononucleosis. In 100% of the observed children receiving viferon, there was a significant decrease in the duration of fever, intoxication, acute tonsillitis, lymphadenopathy, adenoiditis, hepatomegaly, splenomegaly and reduction in hospital stay.

Keywords: Epstein–Barr virus; VEB mononucleosis; younger children; school children; recombinant interferon; viferon.

ВЭБ-МОНОНУКЛЕОЗ НА ГОСПИТАЛЬНОМ ЭТАПЕ: КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА И ЭТИОТРОПНАЯ ТЕРАПИЯ У ДЕТЕЙ РАЗЛИЧНОГО ВОЗРАСТА

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ВЭБ-мононуклеоз — актуальная инфекция детского возраста. Нами проанализировано 764 медицинские карты стационарных больных с ВЭБ-мононуклеозом. Сформированы две группы: I группу (младшего возраста) составили 411 человек (от 1 года до 7 лет), II группу (школьного возраста) — 353 человека (от 7 до 17 лет). В I группе преобладали мальчики, пик госпитализации приходился на весенний период, во II группе — девочки, подъем госпитализации отмечен в зимний период. Преобладали среднетяжелые формы болезни — 684 человека (89,5 %). Тяжелые формы болезни превалировали у детей II группы. В I группе заболевание начиналось остро, а во II группе — подостро. В обеих группах наблюдался весь синдромокомплекс ВЭБ-мононуклеоза: лихорадка, интоксикация, острый тонзиллит, лимфаденопатия. Поражение носоглотки и гепатоспленомегалии чаще встречалось в I группе. При этом увеличение размеров печени и селезенки было до 2 см в зависимости от возрастной нормы. В биохимическом анализе крови выявлено повышение активности АЛТ с одинаковой частотой в обеих возрастных группах. В I группе наблюдалась умеренная активность АЛТ, во II группе — более значительная. В клиническом анализе крови у большинства больных в обеих возрастных группах регистрировали лейкоцитоз. Лимфоцитоз чаще встречался у детей I группы. Моноцитоз чаще фиксировали у детей

II группы. Повышенная СОЭ отмечалась в обеих группах с одинаковой частотой. Атипичные мононуклеары у детей I группы появлялись на первой, а в старшей группе — на второй неделе болезни. Для диагностики ВЭБ-мононуклеоза был использован комплекс лабораторных методов. У 100 % детей, получавших виферон, наблюдалось существенное уменьшение длительности лихорадки, интоксикации, острого тонзиллита, лимфаденопатии, аденоидита, гепатомегалии, спленомегалии и сокращение длительности пребывания в стационаре.

Ключевые слова: вирус Эпштейна – Барр; ВЭБ-мононуклеоз; младшие дети; школьники; рекомбинантный интерферон; виферон.

EBV-mononucleosis is predominantly an infection of childhood [2, 5, 6, 10]. The high interest to this infection results from its involvement in pathological processes in different organs and systems, its association with a number of malignancies, lymphoproliferative and autoimmune diseases. Moreover, Epstein–Barr virus contributes to the progression of HIV infection, is a marker for opportunistic infection in AIDS and acts as a trigger factor for the virus-associated hemophagocytic syndrome [2, 8–12]. There are serious diagnostic difficulties in the pre-hospital and hospital stages [1–3, 6, 7]. A differential diagnosis is carried out between EBV-mononucleosis and tonsillitis, sinusitis, pseudotuberculosis, hepatitis, HIV infection, and leukemia [2, 5, 6, 11]. One of the most frequent causes for admission of patients to the hospital is nasopharyngitis, which is similar to the symptoms of ear, nose, and throat inflammation of different etiology [1–3]. Hepatosplenomegaly with hepatic hyperenzymemia is detected in 10%–90% of EBV-mononucleosis cases [1, 4, 8, 11]; therefore, a differential diagnosis must be initiated between EBV-mononucleosis and hepatitis. Hemogram changes like lymphocytosis and atypical mononuclear cells, which are characteristic to EBV-mononucleosis, are found in 50%–90% of the cases; however such changes are also observed in other respiratory infections [1, 4, 6, 7]. Considering that in the majority of healthy population, the virus can be excreted with saliva and mononucleosis can be asymptomatic, a complex of laboratory diagnostic methods is used to verify the etiology of infectious mononucleosis and determine the stage of the disease [1, 2, 6, 7, 10].

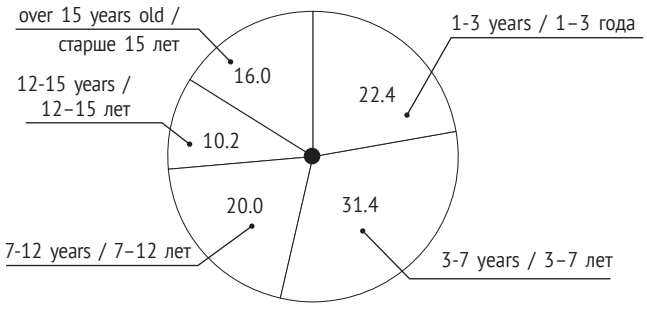

Fig. 1. Age composition of children (%) with VEB mononucleosis
Рис. 1. Возрастной состав детей (%), больных ВЭБ-мононуклеозом

The aim of this study is to evaluate the clinical efficacy of Viferon drug in a complex therapy in children with EBV-mononucleosis.

MATERIALS AND METHODS

764 medical records of hospitalized children with EBV-mononucleosis at the Department of infectious diseases No. 1 of the Saint Petersburg State Pediatric Medical University clinic in 2016–2017 period. The majority of the hospitalized children were in the 3–7 years age interval (n = 240, 31.4%). The hospitalized patients with EBV-mononucleosis were divided into two groups: group I with 411 patients (53.8%) aged 1–7 years (mean age = 3.8 ± 0.1 years), and group II with 353 school-age children (46.2%) aged 7–17 years (mean age = 11.9 ± 0.2 years) (Fig. 1).

RESULTS AND DISCUSSION

In the group I, boys were affected more frequently (n = 259, 63.0%) than girls (n = 152, 37.0%), whereas in the group II, girls were affected more frequently (n = 202, 57.3%) than boys (n = 151, 42.7%).Patients in group I were more frequently hospitalized in spring. In group I, 219 patients (53.3%) were admitted to the hospital in spring, 94 patients (22.9%) in winter, 69 patients (16.8%) in autumn, and 29 patients in summer (7.0%). Patients in group II were more frequently admitted to the hospital in winter. In the group II, 140 patients (39.6%) were hospitalized in winter, 109 patients in spring (30.9%), 81 patients in autumn (23.0%), and 23 patients in summer (6.5%).

Patients admitted to the hospital with the diagnosis “infectious mononucleosis” were 188 patients (45.7%) in group I, whereas they were only 95 patients (26.9%) in group II. In contrast, more patients in the group I were admitted to hospital with the diagnosis of “lacunar tonsillitis” (132 patients, 37.4%) than in group II (78 patients, 19.0%). The remaining patients were referred to the hospital with other diagnoses, such as pseudotuberculosis (n = 88, 11.5%), ARVI (n = 77, 10.1%), and ARVI with exanthema (n = 106, 13.9%).

320 patients (77.8%) in group I and 154 patients (43.6%) in group II were admitted to the hospital at week 1 of onset of the disease (average on day 6). At week 2–3 of onset of the disease (average on day 11), the number of patients in group II ($n = 199$, 56.4%) admitted to the hospital were higher than in group I ($n = 91$, 22.2%). The moderate form of disease was predominant in both groups: 392 cases in group I (95.4%) and 292 cases in group II (82.7%). The severe form of disease was more often noted in patients of the older group, with 61 cases (17.3%) against 19 cases in group I (4.6%).

While analyzing the clinical presentation of the disease, the acute onset of the disease was detected in 63% of children ($n = 483$), with a reparition of 328 patients (79.8%) in group I, and 155 patients (43.9%) in group II. In 281 patients (36.8%), a subacute onset of the disease was observed with gradually increasing fever and intoxication, 83 patients (20.2%) and 198 patients (56.1%)in group I and II accordingly. All patients had typical EBV-mononucleosis syndromes. From day 1 of the disease, sickness syndrome was observed in all patients in both groups, which was characterized by loss of appetite, weakness, and apathy.

Fever was recorded in 726 patients (95.0%), whereas in 38 patients (5.0%) the body temperature remained normal. In both groups, fever characterized by febrile numbers (38.0–39.0 °C) was registered in 261 patients (63.5%) and 204 patients (57.8%) in groups I and II respectively. The fever average duration was 7.1 ± 0.6 and 11.7 ± 0.7 days in group I and group II, respectively.

Acute tonsillitis was also registered in all patients. There were 263 patients in group I (64.0%) and 271 patients in group II (76.8%) who complained of the sore throat when swallowing and with exudative plaques primarily on the palatine tonsils. Inflammatory changes in the oropharynx were limited to catarrhal signs in 87 patients (21.2%) in group I and 36 patients (10.2%) in group II. Hyperplasia I–II of the tonsils was registered in 248 cases in group I (60.3%) and in 181 cases (51.3%) in group II. Older patients are more likely to develop hyperplasia II–III of the tonsils, 135 patients (38.2%) and 92 patients (22.4%), in group I and II respectively. Acute tonsillitis persisted longer in the group II and lasted for 9.5 ± 0.7 days as opposed to 5.9 ± 0.5 days in group I. A microbial exam of the flora oropharyngeal mucous revealed a various bacterial flora in 47.4% of patients with EBV-mononucleosis. *Staphylococcus aureus* prevailed in both groups, namely 67 patients (32.0%) in the group I and 52 (34.0%) in the group II. Pathogenic streptococci were more often found in the patients of the group I ($n = 69$, 33.0%), and *P. aeruginosa* in 12 patients (7.8%) and *H. influenzae* in 9 patients (5.9%) in the group II. Combined flora was more common in group II (27 patients, 17.6%) than that in the group I (14 patients, 6.7%).

Inflammation of the pharyngeal tonsil was observed in 531 patients with EBV-mononucleosis (69.5%) and was accompanied by nasal congestion, impaired nasal airflow with scarce discharge, rasping, and stertorous breathing through the mouth, snoring during sleep, face puffiness, and the eyelids swelling. All manifestations of adenoiditis were more common in the group I ($n = 358$, 87.1%) than in the group II ($n = 173$, 49.0%). The duration of adenoiditis was shorter in the group I; for instance, it lasted for 6.2 ± 0.4 days in group I compared to its duration of 7.6 ± 0.5 days in the group II.

Lymphadenopathy occurred in all patients. From day 1 of the disease, the lymph nodes mostly of the cervical group: anteroposterior and posterior were affected; 277 patients (67.4%) and 310 patients (75.4%) in group I, 223 patients (63.2%) and 168 patients (47.6%) in group II, respectively. In addition, other lymph nodes were also involved in the pathological process of EBV-mononucleosis. Supramandibular lymph nodes were affected in 56 patients in group I (13.6%) and 41 patients in goup II(11.6%); inguinal lymph nodes were affected in 43 cases in group I (10.5%) and 39 cases in group II (11.0%). Axillary lymph nodes were significantly affected in patients in group II, i. e., 61 cases in group II (17.3%) against 21 cases in group I (5.1%). Lymph nodes were painless, dense, with a round-shape or chain-like configuration. Upon visualization, the lymph nodes were from 2 to 6 cm in diameter and the skin color over them did not change. The duration of lymphadenopathy syndrome in the groups I and II pediatric patients were 9.4 ± 0.6 and 15.0 ± 0.7 days, respectively.

Simultaneous involvement of the liver and spleen in the pathological process was present in every second or third patient ($n = 455$ patients, 59.6%). Hepatomegaly syndrome was registered in a total of 511 patients (66.9%), 314 in group I (76.4%) and 197 in group II (55.8%). In most cases, its edge protruded 1–2 cm from under the costal arch in 187 (59.6%) and 101 (51.3%) patients in groups I and II respectively. Patients complained of abdominal pain, as well as mild tenderness of the liver during palpation. Hepatomegaly syndrome was more prolonged in the group II and lasted for 16.8 ± 0.9 days, compared with 9.9 ± 0.7 days in the group I. Upon admission to the hospital, a total of 621 patients (81.3%) with EBV-mononucleosis manifested an increase in ALT activity: 344 cases in group I (83.7%), and 277 cases

in group II (78.5%). Moderate ALT activity (from 40.0 to 100.0 U/l) was noted in 208 patients in group I (50.6%) and 111 patients in group II (31.4%). In the school-age group (group II), there was a significant hyperenzymemia (200 U/l and higher) in 92 patients (26.1%) against 29 patients (7.1%) in the group I. The average indicators in the group I amounted to 74.6 ± 5.9 U/l, whereas they were 169.3 ± 14.2 U/l in the group II.

Splenomegaly syndrome was present in a total of 372 patients (48.7%), primarily in group I (63.5%) by the end of week 1 of the disease. Patients from both groups manifested an increase in the spleen size that did not exceed 2 cm, 152 patients (58.2%) in group I and 71 (64.0%) in group II. However, the duration of splenomegaly syndrome was longer in group II than that in group I (9.2 ± 0.6 days versus 6.4 ± 0.5 days in group II and I, respectively).

A blood test in patients with EBV-mononucleosis showed that in 650 patients (85.1%), there was an increase in the leukocyte count, in 348 patients (84.7%) and patients (85.6%) in group I and group II respectively. It was noted that a total of 114 patients (14.9%) had normocytosis, 63 patients (15.3%) in group I and 51 patients (14.4%) in group II. Lymphocytosis in EBV-mononucleosis was registered in 345 patients (45.2%), in group I- 203 patients (49.4%) and in group II-142 patients (40.2%). Monocytosis was more common in school-aged patients (197 patients or 55.8%) than in patients in the younger age group (124 patients, 30.2%). Atypical mononuclear cells (AMCs) were recorded in 515 patients (67.4%), and their number varied within a wide range from 1% to 51%, namely in group I-314 patients (76.4%) (average 18.4 ± 0.9%); and in group II-201 patients (56.9%) (average 24.9 ± 1.1%). AMCs were detected at different terms after the onset of the disease. At week 1 of the disease, AMCs were noted in 281 patients (54.6%), with a proportion of 228 patients (72.6%) in group I and 53 patients (26.4%) in group II. At week 2, AMCs were found in 147 patients (28.5%) (49 patients in group I and 98 in group II) and. At week 3, AMCs were found in 87 patients (16.9%); in group I-37 patients (11.8%) and in group II-50 patients (24.8%). Thus, in the group I, AMCs appeared at early stages of the disease, and at later stages in the group II patients. The erythrocyte sedimentation rate (ESR) was 2–50 mm/h. Increased ESR was observed in 186 patients in group I (45.3%) and in 182 patients in group II (51.6%) (an average of 30.4 ± 3.5 and 39.8 ± 2.4 mm/h, respectively).

Specific antibodies EBV–IgM were found in almost all patients: 371 patients in group I (90.3%) and 339 patients in group II (96.0%).

PCR was used to determine the EBV DNA in patients' blood & saliva samples. In almost half of the patients (n = 364, 47.4%), EBV DNA was detected in the saliva and blood of patients; group I-195 patients (47.4%) and 169 patients in group II (47.9%). The EBV DNA was only detected in the saliva of 183 patients (24.0%); in group I-83 patients (20.2%) and in group II-100 patients (28.3%), and only in the blood of 133 patients in group I (32.4%) and 84 patients in group II (23.8%).

In therapy, patients were randomized into two groups. The study group comprised patients who received aetiotropic treatment with Viferon and background therapy, group I: younger- age group of 156 patients (38.0%) and group II: school-age group of 101 patients (28.6%). The comparison group included a similar number of patients of both ages who received only background therapy. Viferon, which is human recombinant interferon α-2b with antioxidants (vitamin C and vitamin E), was prescribed based on the following scheme: 150,000 IU administered twice a day in the group aged 1–7 years (group I), and 500,000 IU twice a day in the group aged 7–17 years (group II); the course therapy lasted 5 days.

The analysis of the clinical efficacy of Viferon showed clear positive dynamics of clinical symptoms in all patients with EBV-mononucleosis (Fig. 2, 3). Compared with patients who received only background therapy. All patients who received Viferon showed a significant decrease in the duration of fever, intoxication, acute tonsillitis, lymphadenopathy, adenoiditis, hepatomegaly, and splenomegaly. In patients treated with Viferon, the average stay in the hospital was 6.1 days in group I (8.2 days in the comparison group), and 6.2 days in group II (8.3 days in the comparison group).

Following hospital discharge, the 3-month follow-up showed a smooth course of late recovery period in both groups who received Viferon. On the contrary, an unsmooth course of the disease was observed in 26,3% cases among patients of the comparison group (subfebrile condition in 6.3% of cases, lymphadenopathy in 2.9% of cases, and deposit ARVI in 17.1% of cases).

CONCLUSION

EBV-mononucleosis in children of different ages (from 1 year to 17 years) occurs in moderate form (89.5%) with a characteristic syndrome complex: fever, intoxication, acute tonsillitis, adenoiditis, lymphadenopathy, hepatosplenomegaly. Most of the patients were hospitalized within winter and spring periods; EBV-mononucleosis incidence was high in boys from the younger-age group, and girls from the school-age group. Patients of group I were admitted to the hospi-

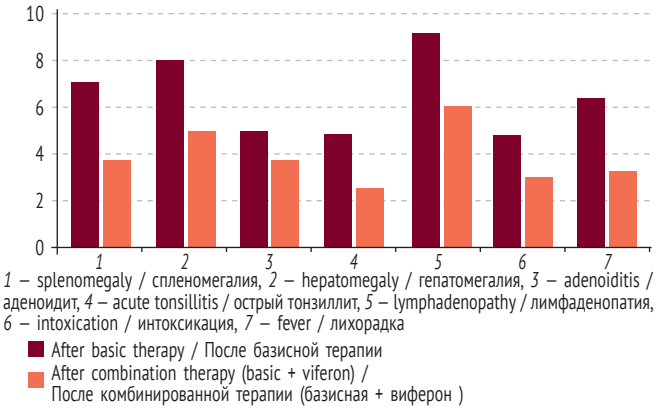

Fig. 2. Clinical efficacy of viferon in young children with VEB mononucleosis (days)

Рис. 2. Клиническая эффективность виферона у детей младшего возраста, больных ВЭБ-мононуклеозом (сутки)

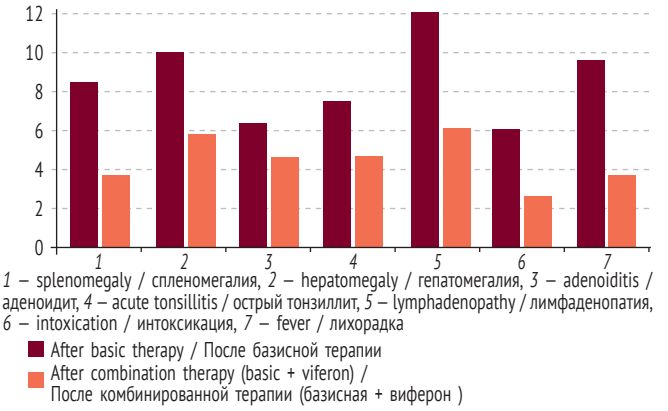

Fig. 3. Clinical efficacy of viferon in school-age children with VEB mononucleosis (days)

Рис. 3. Клиническая эффективность виферона у детей школьного возраста, больных ВЭБ-мононуклеозом (сутки)

tal more often at week 1 of the onset of the disease, and those of group II were admitted at weeks 2 and 3.

When Viferon was included in the therapy for EBV-mononucleosis, the duration of all clinical syndromes was significantly reduced compared with patients who received only background therapy. In young children, the duration of fever period was reduced by 2 times. Manifestations of sickness syndrome significantly decreased by the day 3–4 of the disease. The duration of the lymphoproliferative syndrome (lymphadenopathy, acute tonsillitis, adenoiditis, and hepatosplenomegaly) was also significantly reduced by 1.5–2 times. School-age patients who received Viferon had even earlier remarkable positive changes of the main clinical syndromes.

In our study, Viferon therapy helped to reduce the duration of all-age patients' stay in the hospital and reduce the economic burden of treatment.

During therapy with Viferon, a smooth course of EBV-mononucleosis was noted in the period of clinical manifestations (absence of complications) and in the long-term period (absence of ARV superinfection during 3-month follow-up). No adverse reactions and events were registered in the usage of Viferon.

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