

THE INFLUENCE OF THE EPSTEIN-BARR VIRUS ON PARACLINICAL INDICATORS AND CYTOKINE LEVELS IN CHILDREN WITH ROTAVIRUS GASTROENTERITIS

Marharyta Sliepchenko, Olga Olkhovska

The aim. To identify the influence of the latent form of Epstein-Barr virus infection on the clinical picture, parameters of clinical blood analysis and cytokine response of children with rotavirus gastroenteritis.

Materials and methods. 56 children were examined. Of them, 33 children (group 1) had no background infection with herpesviruses, and 23 patients (group 2) suffered from rotavirus gastroenteritis against the background of Epstein-Barr virus (EBV) infection. The patients were comparable in terms of sex, age and disease severity. Differences at $p < 0.05$ were considered statistically significant.

Results. The analysis of the obtained data showed that the latent form of EBV infection affects the clinical picture, indicators of clinical blood analysis and the reaction of serum cytokines of children with rotavirus gastroenteritis.

Conclusions. A comparative analysis revealed that a latent form of herpesvirus infection in children with rotavirus gastroenteritis is associated with lower temperature reaction and a lower frequency of vomiting in the acute period of the disease against the background of longer persistence of fever, diarrhoea and catarrhal syndromes. On the part of the investigated laboratory indicators, the presence of EBV infection is characterized by a lower level of haemoglobin ($p=0,013$) against a higher content of neutrophils ($p=0.002$), eosinophils ($p=0.033$) and monocytes ($p < 0.001$) in the acute period of RVI, and a significantly higher content of eosinophils ($p=0.001$) and monocytes ($p < 0.001$) against the background of a lower level of the relative content of lymphocytes compared to patients of Group 1 in the period of early convalescence. Changes in the cytokine response in children with mixed infection are characterized by a significantly lower concentration of IL-1 β at the onset of RVI and a higher content of IL-4 and TNF- α throughout the disease compared to children with mono-RVI

Keywords: Children, rotavirus infection, Epstein-Barr virus, clinic, components of complete blood count, cytokines

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1. Introduction

Acute intestinal infections of viral aetiology, characterized by the rapid development of ecchymosis, are an urgent problem in paediatrics. In the structure of viral diarrhoea in children, rotavirus occupies the first place. Despite the widespread use of vaccination to prevent rotavirus infection (RVI), about 125 million cases of rotavirus gastroenteritis are registered annually in the world [1]. Another problem of modern infectiology is latent herpesvirus infection (HVI), its influence on the host's immune response and the course of other infectious diseases [2, 3]. Some scientists consider herpesviruses (HV) as a factor that negatively affects the course of other diseases and contributes to the development of oncopathology. In contrast, other researchers, on the contrary, describe the immunomodulating effect of HV [4, 5]. Furthermore, some authors consider the Epstein-Barr virus (EBV) as a pathogen that promotes blast transformation of B cells, complicates the course of nonspe-

cific ulcerative colitis, Crohn's disease, and causes the development of urticaria [6, 7]. And other authors note that VEB infection reduces the risk of developing bronchial asthma and ensures the development of heterologous cross-immunity [8, 9].

Usachova O.V. et al. (2013) studied the effect of HV on the course of rotavirus infection but analyzed only clinical differences and did not study laboratory parameters, which in turn can, at least partially, deepen knowledge of the mechanism of HV's influence on the course of RVI [10]. In the available literature, there are works devoted to studying the cytokine response in patients with RVI. However, their results are contradictory, which may be related to each study design [11, 12]. The difficulty of studying the effect of latent EBV infection on the immune response is due to the high level of seropositivity to EBV and other EBV among the population; therefore, in our opinion, the study of children from 1 to 3 years of age has certain advantages, because some

children are infected at this age. This makes it possible to include in the control Group patients who are not yet infected with viruses of the herpes group. Considering the important role of cytokines in the formation of the immune response and the course of the disease, we decided to investigate the content of some of them (IL-1 β , IL-4, TNF- α) in children with rotavirus gastroenteritis. We also decided to analyze the indicators of peripheral blood, the study of which is the most widespread and accessible analysis performed for every child upon admission to the hospital and the results of which can provide valuable information. In the future, the established differences can be included in the algorithm for diagnosing the latent form of EBV infection in children with rotavirus gastroenteritis based only on clinical and para-clinical indicators.

Studying the parameters of clinical blood analysis and cytokine content at the onset of the disease and during early convalescence will contribute to understanding the features of the immune response of patients to rotavirus antigens in the presence of EBV infection in children.

The aim. To identify the influence of the latent form of Epstein-Barr virus infection on the clinical picture, parameters of clinical blood analysis and cytokine response of children with rotavirus gastroenteritis.

2. Materials and methods

The study involved the supervision of 56 children aged from 12 to 36 months (median age 24.0 [19.0; 30.0]), patients with moderate and severe intestinal infections of rotavirus aetiology, for which they received appropriate treatment in Kharkiv Regional Children's Infectious Diseases Clinical Hospital from September 2018 year to January 2020 year. The first group included 33 children suffering from rotavirus gastroenteritis without co-infection with EBV (mono-RVI). The second group consisted of 23 children who suffered rotavirus infection against the background of co-infection with EBV. When forming groups, inclusion and exclusion criteria were used. Inclusion criteria: age of children from 12 to 36 months, laboratory-confirmed diagnosis of rotavirus infection, with the help of isolation of rotavirus antigen from the faeces of patients with the help of test systems CITO TEST ROTA-ADENO (immunochromatographic method) (OOO "Pharmasco", Ukraine), positive result for specific IgG to EBV capsid antigen, presence of informed consent of parents to participate in the study. Exclusion criteria: the age of children younger than 12 months or older than 36 months, the presence of a positive result for bacterial and other viral pathogens of intestinal infections, the presence of IgM and/or IgG specific to other viruses of the herpes group (HSV 1,2, CMV, HHV-6 type), a positive result of qualitative PCR for the determination of EBV DNA, and the presence of severe background pathology. The study groups are comparable in terms of gender, age, disease severity and other parameters. The first group included 15 (45.5 %) girls and 18 (54.5 %) boys; the second group included 14 (60.9 %) girls and 9 (39.1 %) boys, $\chi^2=1.290$, $p=0.256$. The median age in group 1 is 23.0 [19.0; 26.0] months, and in Group 2 – 28.0 [23.0; 31.0] months, $p=0.060$. RVI of medium-severe form was diagnosed in 15 (45.5

%) children of the first group and 12 (52.2 %) of the second; 18 (54.50 %) patients of the first group and 11 (47.8 %) of the second group had a severe course, $\chi^2=0.245$, $p=0.620$. All patients in the acute period (1–3 days) and the period of early convalescence (7–10 days) underwent a standard clinical blood test and assessed the reaction of blood cytokines (IL-1 β , IL-4, TNF- α pg/ml, cytokine concentration were determined by the solid-phase immunoenzymatic method using standard sets of reagents "Vector Best" Ukraine, according to the instructions).

Examination of patients was performed if parents provided written informed consent. Commission with of ethics and bioethics of Kharkiv National Medical University (protocol No. 7 dated September 11, 2018) established: the research methods comply with the current legislation of Ukraine and the requirements of the World Medical Association's Helsinki Declaration, do not violate ethical standards in science and standards for conducting biomedical research.

All patients in the acute period (1–3 days) and the period of early convalescence (7–10 days) underwent a standard clinical blood test and assessed the reaction of blood cytokines (IL-1 β , IL-4, TNF- α pg/ml, cytokine concentration were determined by the solid-phase immunoenzymatic method using standard sets of reagents "Vector Best" Ukraine, according to the instructions). The nature of the distribution of quantitative signs was assessed using a visual graphic method and using the Shapiro–Wilk's normality test. Since the evaluation of indicators established significant differences from the normal nature of the distribution, non-parametric statistical methods were used in the calculations. Quantitative values are given as median (Me) and lower (LQ), and upper (UQ) quartiles. In addition, the probability of differences in quantitative indicators in two unrelated groups was also determined using the Mann–Whitney U-test. The critical value of p was considered to be 0.05. Statistical results were processed using the IBM SPSS 25.0® for Windows® (Trial version) application program package. There is no conflict of interest.

3. Research results

The study of the main clinical manifestations established that rotavirus gastroenteritis in children with concomitant EBV infection is characterized by lower temperature reaction numbers ($p < 0.001$), a lower frequency of vomiting ($p=0.002$) at the onset of the disease compared to children in the first group. At the same time, fever ($p < 0.001$), diarrheal ($p < 0.001$) and catarrhal ($p=0.012$) syndromes persisted significantly longer in the patients of the second Group (Table 1).

During the analysis of clinical blood analysis indicators in the acute period of rotavirus infection and in the early convalescence period, no significant differences were found among the comparison groups between the median values of the content of erythrocytes, leukocytes and the erythrocyte sedimentation rate (ESR).

The general trend of changes in indicators of clinical blood analysis during the course of the disease in both groups is unidirectional. However, significant differences were established between individual parameters (Table 2). In the acute period of RVI, the haemoglobin

content in children with concomitant EBV infection was significantly higher compared to children in the first group ($p=0.013$). Also, the presence of concomitant EBV infection during the acute period of rotavirus gastroenteritis is associated with a higher content of rod-shaped neutrophils ($p=0.002$), eosinophils ($p=0.033$) and mono-

cytes ($p < 0.001$). In the period of early convalescence, the content of eosinophils ($p=0.001$) and monocytes (<0.001) remained significantly higher in children of the second group against the background of a lower level of the relative content of lymphocytes compared to patients not infected with EBV.

Table 1

Clinical symptoms of RVI and their duration in children uninfected and infected with EBV Me [LQ; UQ]

Clinical symptoms	Group 1 (n=33)	Group 2 (n=23)	<i>p</i>
Maximal temperature, °C	38,9 [38,8; 39,2]	38,5 [38,4; 38,7]	<0.001
Duration of temperature, days	4,0 [3,0; 4,5]	6,0 [6,0; 7,0]	<0.001
Maximal daily frequency of vomiting	4,0 [3,0; 5,0]	3,0 [2,0;3,0]	0.002
Duration of vomiting, days	1,0 [1,0; 2,0]	1,0 [1,0; 2,0]	0.585
Maximal daily frequency of diarrhoea	5,0 [4,5; 6,0]	5,0 [5,0; 6,0]	0.699
Duration of diarrhoea, days	3,0 [3,0; 4,0]	5,0 [4,0; 5,0]	<0.001
Duration of catarrhal signs, days	3,0 [3,0; 4,0]	4,0 [3,0; 4,0]	0.012

Table 2

Characterization of indicators of clinical blood analysis of children who are not infected and infected with EBV in the acute period (AP) and in the period of early convalescence (CP) of RVI, Me [LQ; UQ]

Indices, units of measurement	Group 1 (n=33)		Group 2 (n=23)		<i>P</i> ₁	<i>P</i> ₂
	AP	CP	AP	CP		
RBC, *10 ¹² /L	4.0 [3.9;4.2]	4.5 [4.2;4.8]	4.0 [3.9;4.3]	4.3 [4.1;4.5]	0.725	0.088
HGB, g/l	112.0 [108.5;120.0]	120.0 [116.0; 123.5]	119.0 [116.0;122.0]	122.0 [120.0;125.0]	0.013	0.198
WBC, *10 ⁹ /l	9.1 [7.5;10.5]	5.6 [5.1;6.4]	8.9 [6.2; 10.2]	5.7 [5.2;6.4]	0.368	0.861
Rod-shaped neutrophils, %	2.0 [1.0;2.0]	2.0 [1.0;2.0]	2.0 [2.0;3.0]	2.0 [1.0;2.0]	0.002	0.762
Segmented neutrophils, %	32.0 [32.0; 41.0]	30.0 [28.0;34.0]	34.0 [25.0; 40.0]	32.0 [28.0;35.0]	0.953	0.293
Eosinophils, %	1.0 [1.0;1.0]	2.0 [1.5;2.0]	2.0 [1.0; 2.0]	3.0 [2.0;3.0]	0.033	0.001
Lymphocytes, %	63.0 [53.0;70.0]	63.0 [60.0;65.0]	58.0 [54.0;67.0]	58.0 54.0; 61.0]	0.443	<0.001
Monocytes, %	2.0 [2.0;3.0]	3.0 [3.0;4.0]	4.0 [3.0; 4.0]	6.0 [5.0;7.0]	<0.001	<0.001
ESR, мм/год	9.0 [6.0;13.0]	8.0 [6.0;10.5]	9.0 [7.0; 12.0]	8.0 [7.0; 9.0]	0.821	0.854

Note: *p*₁ – between indicators of Groups 1 and 2 in the acute period of the disease; *p*₂ – between the indicators of Groups 1 and 2 in the period of early convalescence

Blood cytokine response in children infected with EBV in the acute period of RVI was characterized by significantly lower levels of IL-1 β ($p=0.004$) against a higher concentration of IL-4 ($p<0.001$) and TNF- α ($p<0.001$). However, in the period of early convalescence

in both groups, IL-1 β levels decreased and no longer had significant differences. Instead, the concentration of IL-4 ($p<0.001$) and TNF- α ($p<0.001$) significantly prevailed in children infected with EBV compared to patients of the first Group (Table 3).

Table 3

Indicators of blood cytokine response of comparison groups of patients during the disease, Me [LQ; UQ]

Indices, units of measurement	Group 1 (n=33)		Group 2 (n=23)		<i>P</i> ₁	<i>P</i> ₂
	AP	CP	AP	CP		
IL-1 β pg/ml	21.1 [18.5;24.6]	8.1 [7.3; 9.5]	18.9 [16.9;21.0]	10.2 [8.6;11.7]	0.004	0.007
IL-4 pg/ml	4.9 [3.9;6.2]	12.7 [11.4; 13.9]	8.5 [7.3;9.0]	15.3 [13.2;17.1]	<0.001	<0.001
TNF- α pg/ml	6.3 [5.7;7.1]	4.9 [4.0; 5.3]	11.5 [10.2;12.2]	8.1 [7.5;9.3]	<0.001	<0.001

Note: *p*₁ – between indicators of Groups 1 and 2 in the acute period of the disease; *p*₂ – between the indicators of Groups 1 and 2 in the period of early convalescence

4. Discussion

The established changes in the clinical picture, clinical blood analysis and cytokine concentration are closely related. The data we obtained partially coincide with the results of the research of Usachova O.V. (2013). We also recorded the prolongation of clinical manifestations of RVI, but due to the longer persistence of fever, catarrhal and diarrheal syndromes, and not the addition of damage to the tracheobronchial tree and liver [10]. The existence of discrepancies in the study results can be explained by the fact that the authors studied the effect of β -herpesvirus on the course of rotavirus gastroenteritis, contact with which occurred in the perinatal period. In a study on the impact of EBV on an intestinal infection of bacterial aetiology, the authors also established the prolongation of clinical manifestations, which is consistent with our data [13]. But when comparing indicators of clinical blood analysis and cytokine response, discrepancies were found, which are probably caused by the bacterial aetiology of the intestinal infection under study [14].

According to many authors, latency of herpesvirus infection involves the cyclic reactivation of herpesviruses, which leads to the activation of cytotoxic lymphocytes, which in turn contribute to the synthesis of TNF- α and already together ensure the apoptosis of infected cells [4, 15]. In parallel with this, we observe a higher level of monocytes in children infected with EBV, which in turn can also produce TNF- α and take an active part in the elimination of the pathogen [12, 16]. The above, from our point of view, is the reason for significantly higher levels of TNF- α in the children of the second group. The increased concentration of IL-4 in children with co-infection with EBV, in our opinion, is associated with the activation of the humoral link of the immune response, which prevents the infection of new cells with the virus, as indicated by other authors [11, 17]. Also, at the current stage, HV antigens are considered allergens that contribute to the sensitization of the body [8, 9]. This subclinical sensitization is characterized by immune changes characterized by increased histamine, IgE, eosinophils, and IL-4. In our work on children infected with EBV, we observed an increased content of not only IL-4 but also eosinophils. Therefore, the increase of IL-4 in the blood serum of children infected with EBV can be caused by key factors.

The lower content of IL-1 β , in the acute period of RVI, in children infected with EBV most likely, is associated with the antagonistic effect of anti-inflammatory IL-4 on it, which is probably the reason for lower numbers of temperature reactions and frequency of vomiting in patients of the group 2 [9, 17]. Comparing the response of cytokines in the blood of the examined children with the results of other researchers who studied the concentration of cytokines in the blood of EBV-infected patients with acute respiratory infections, Crohn's disease, allergic pathology, we recorded coincidences, which consisted in the increased content of IL-4 and TNF- α [4, 11, 12, 14]. This gives reason to believe that the presence of a latent form of EBV infection is associated with an imbalance of pro- and anti-inflammatory cytokines.

Changes in the level of haemoglobin in patients with an acute infectious process are due to the develop-

ment of the so-called infection-associated anaemia [18]. Some authors even consider a decrease in haemoglobin as a marker of an unfavourable course of the disease, while others have established a reliable negative correlation between the level of haemoglobin and the content of leukocytes, which, along with other parameters, characterizes the intensity of the immune response to the pathogen [19, 20]. Thus, we believe that higher haemoglobin levels in children with co-infection with EBV are due to a less pronounced intensity of the inflammatory process compared to patients with mono-RVI, in whom at the onset of the disease, significantly higher temperature response numbers, a higher frequency of vomiting and higher levels of pro-inflammatory cytokines were established IL-1 β . In our opinion, the increased content of neutrophils in the acute period of RVI in children infected with EBV is associated with a more pronounced activation of phagocytosis [4, 21]. There are studies that concluded that the presence of a viral infection could prolong the duration of neutrophil circulation [22].

In the period of early convalescence, the levels of lymphocytes, eosinophils and monocytes remain significantly elevated, which is probably related to the presence of a mixed viral infection in the elimination of which these cells take an active part. Also, from our point of view, higher levels of lymphocytes, eosinophils and monocytes in the period of early convalescence, together with the increased content of TNF- α , determine the prolongation of the inflammatory process, namely, the longer persistence of fever, diarrhoea and catarrhal syndromes.

The results of the conducted research may have diagnostic value for doctors in the practical field of health care. If the duration of diarrhoea is more than 5 days and the temperature is more than 6 days against the background of the level of peripheral blood monocytes above 6 % and eosinophils above 3 % in the early period of convalescence, RVI is a reason for further examination of the patient for the presence of EBV infection. As you know, many factors, including concomitant infectious diseases, can lead to the activation of latent EBV infection, which affects the state of the immune system and can lead to adverse consequences.

Study limitations:

1. Small sample size.
2. The inability to extrapolate the obtained data to patients younger than 1 year or older than 3 years.

Prospects for further research. The results of the study can be used to develop a model for predicting the presence of latent EBV infection in children with rotavirus gastroenteritis.

5. Conclusions

1. Rotavirus infection occurring on the background of EBV infection is characterized by lower temperature reaction numbers and a lower frequency of vomiting in the acute period of the disease against the background of longer persistence of fever, diarrhoea and catarrhal syndromes.

2. The presence of EBV infection, in children with RVI, from the clinical blood analysis, is associated with a lower level of haemoglobin against the background of a higher content of rod-shaped neutrophils

($p=0.002$), eosinophils ($p=0.033$) and monocytes ($p < 0.001$) in the acute period RVI. In the period of early convalescence, the content of eosinophils ($p=0.001$) and monocytes ($p < 0.001$) was significantly higher against the background of the lower level of the relative content of lymphocytes compared to patients of Group 1.

3. The cytokine response of the blood of patients infected with EBV is characterized by a significantly lower concentration of IL-1 β at the onset of RVI and a higher content of IL-4 and TNF- α throughout the disease compared to children with mono-RVI.

Conflict of interest

The authors declare that there is no financial, personal, authorial or another conflict of interest that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request

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