Clinical and immunological features of rotavirus infection in children infected with Epstein-Barr virus.

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ABSTRACT

The aim: to identify clinical and immunological features of acute rotavirus gastroenteritis occurring against the background of Epstein-Barr virus infection.

Materials and methods: The study involved examination of 56 children. Of them, 33 children (1 group) did not have a background infection and 23 patients (2 group) suffered from rotavirus infection on the background of the latent form of Epstein-Barr virus infection. Children in these groups were compared by gender, age, severity of the disease and other parameters.

Quantitative data were presented as mean and standard deviation (M±SD). Differences at $p < 0.05$ were considered statistically significant.

Results and conclusions: The data suggest that the presence of background Epstein-Barr virus in children with rotavirus infection leads to later hospitalization, lower temperature response rates, lower frequency of vomiting at the onset of the disease, and longer duration of fever and diarrhea. At the same time, in children infected with Epstein-Barr virus, the relative content of $CD8^+$ T lymphocytes dominated both in the acute period of the disease and in the period of convalescence against the background of reduced relative content of $CD16^+$, $CD22^+$ T lymphocytes and IgM in the period of early convalescence.

Key words: latent Epstein-Barr infection, acute rotavirus gastroenteritis, intracellular pathogens.

Introduction

In the structure of morbidity of the gastrointestinal tract of infectious nature, rotavirus infection (RVI) occupies one of the leading places among infants and young children [1, 2]. In the available literature there is a large number of studies devoted to the assessment of the clinical picture of RVI [3]. However, recently there have been publications in which scientists point to changes in clinical symptoms and the course of RVI, which researchers associate with a number of causes of exogenous and endogenous nature [2, 3]. A number of authors consider mass infection of children with Herpes viruses to be one such reason, which can affect the patient's immune response [4, 5]. Herpes viruses, which children become infected with in the first years of life, also include Epstein-Barr virus (EBV) [6, 7]. The mechanisms of interaction between EBV and the immune system of the macroorganism have been studied by many scientists, but their conclusions differ [4, 5, 8]. Some authors point to the lack of influence of EBV on the immune response, others believe that the presence of EBV in a child can lead to suppression of the functional activity of its immunocompetent organs and the development of immunosuppressive state [9, 10, 11]. At the same time, some scientists report beneficial, immunomodulatory effects of lifelong interaction between the virus and the immune system, considering the relative uniqueness of EBV-specific $CD4^+$ and $CD8^+$ T-cells to be the evidence of the latter, which is the ability to activate in response to other pathogens in physiologically relevant method and determine the development of heterologous cross-immunity [12].

Changes in the clinical picture of RVI in recent years, differences in the results of studies of the immune response of children in this disease and the possible impact of EBV, became an argument in favor of conducting research in this direction.

The purpose of the study: to identify clinical and immunological features of rotavirus infection in children infected with Epstein-Barr virus.

Materials and methods

The study involved supervision of 56 children aged one to three years, patients with moderate and severe intestinal infections of rotavirus etiology, for which they received appropriate treatment in Kharkiv Regional Children's Infectious Diseases Clinical

Hospital. Of them, 33 children (first group) did not have a background infection and 23 patients (second group) suffered from RVI on the background of the latent form of EBV. The criteria of the inclusion of children in the study groups were the diagnosis of acute intestinal infection caused by rotavirus for the first group, and both acute intestinal infection caused by rotavirus and latent EBV infection for the second group. Verification of RVI diagnosis was carried out by isolating rotavirus antigen from the feces of patients by enzyme-linked immunosorbent assay (ELISA) and the corresponding IgM antibodies in the blood. The presence of latent EBV infection was established in the presence of specific antibodies IgG to EBV in the serum of children and in the absence of IgM (ELISA) and nucleic acid (PCR) of herpesviruses types 1, 2, 4, 5, 6. The criteria of the exclusion: positive results for bacterial and viral pathogens of intestinal infections, except rotavirus; latent herpesviruses infection (positive specific IgG to herpesviruses types 1, 2, 5, 6) or active herpesviruses infection (positive result to specific IgM or/and nucleic acid of herpesviruses types 1, 2, 4, 5, 6) and children with somatic background diseases.

Children in these groups were compared by gender, severity of the disease and age. 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, $\chi 2 = 1,290$, $p = 0.256$. At the same time, 15 (45.50%) children from the first group and 12 (52.2%) from the second group suffered from moderate form of RVI, and 18 (54.50%) patients from the first group and 11 (47, 8%) from the second, suffered RVI in a severe form $\chi 2 = 0.245$, $p = 0.620$. The average age in group 1 was 23,3±5,2 months, and in group 2 was 26,1±7,2 months, $p = 0,06$.

The Vesicari score was used to determine the severity of rotavirus gastroenteritis. This scale takes into account the frequency and duration of diarrhea and vomiting, the level of temperature response, as well as the degree of dehydration of the patient and the level of medical care. Each of these indicators is evaluated in points, and the sum of points is then used to assess the severity of the disease. Mild

disease is diagnosed with a score of <7, moderate from 7 to 10 points, and severe with a score of > 11.[13].

The Commission on Ethics and Bioethics of Kharkiv National Medical University (Protocol No.7, dated 11 September 2018) Research was conducted in accordance with the World Medical Association's Helsinki Declaration.

The generally accepted laboratory tests (general blood test, general urine analysis, coprogram and bacteriological examination of feces), given in the Order of the Ministry of Health of Ukraine No. 803 of 10.12.07 "Protocol for the treatment of acute intestinal infections in children" were carried out. In addition to generally accepted laboratory tests, patients underwent immunological tests. The content of lymphocytes CD3 +, CD4 +, CD8 +, CD16 +, CD22 + in blood serum was also determined by immunofluorescence method using monoclonal antibodies (GRANUM, Ukraine) during the time course of the disease (1-2 and 8-10 days). The immunoregulatory index (IRI) was calculated as the ratio of the relative CD4 + / CD8 + content. The content of immunoglobulins of class A, M, G (IgA, IgM, IgG) (g/l) of blood serum was determined using two-site enzyme-linked immunosorbent assay (sandwich method) (GRANUM, Ukraine).

Statistical analysis was performed using IBM SPSS 25.0 statistical software package. Continuous data were reported as M±SD. Significance between two independent variables was calculated using Mann-Whitney U-test, significance between two related variables was calculated using Wilcoxon matched-pair signed-rank test. Critical α-error value was 0.05, thus the result was considered statistically significant in $p < 0.05$. Exact two-sided p-values were reported.

Results

The clinical picture of RVI, in almost 100% of cases, was characterized by fever, recurrent vomiting, frequent liquid stools without pathological impurities. Moreover, 78% of patients had catarrhal manifestations (serous discharge from the nose, coughing, hyperemia of the mucous membrane of the posterior pharyngeal wall). Assessment of literature data and the results of our own observations suggest

preservation of the overall clinical symptoms of RVI in children at present. However, the severity of the above clinical manifestations of the disease and their duration was probably determined by the background condition of the child, including, in our opinion, the presence of infection of the patient with EBV (Table I).

A total of 56 children were examined. Group 1 included 33 children, of whom 15 (45.5%) had moderate to severe and 18 (54.5%) had severe condition ($p = 0.602$). Group 2 included 23 patients, of whom 12 (52.2%) had moderate and 11 (47.8%) severe disease ($p = 0.835$). The mean age of patients in Group 1 was 23.30 ± 5.25 months and 26.08 ± 7.20 months in Group 2 ($p = 0.060$). There were no gender differences among the comparison groups, $p = 0.602$ in Group 1 and $p = 0,297$ in Group 2.

Table I

Clinical symptoms of RVI and their duration in children uninfected and infected with EBV **(M±SD)**

Clinical symptoms	**Group 1 (n=33)**	**Group 2 (n=23)**	***p***
Maximal temperature, °C	39.04±0.48	38.5±0.31	***<0.001***
Duration of febrile temperature, days	3.00±0.86	4.26±0.54	***<0.001***
Duration of subfebrile temperature, days	1.00±0.70	2.00±0.52	***<0.001***
Maximal daily frequency of vomiting	4.21±2.23	2.38±1.43	***0.002***
Duration of vomiting, days	1.36±0.74	1.17±0.83	*0.330*
Maximal daily frequency of diarrhea	5.39±1.54	5.21±1.38	*0.817*
Duration of diarrhea, days	3.57±0.79	4.52±0.84	***<0.001***
Duration of catarrhal signs, days	3.36±1.03	3.60±0.65	*0.223*

Assessment of temperature response showed that in patients of Group 2 the average maximum body temperature at the onset of the disease was significantly lower than in patients of Group 1 (38.5 ± 0.31 C, 39.04 ± 0.48 C, $p < 0.001$). However, the duration of febrile fever in them was almost one and a half times (4.26 ± 0.54 days and 3.00 ± 0.86 days, $p < 0.001$), and subfebrile temperature (2.00 ± 0.52 days and 1.00 ± 0.70 days, $p < 0.001$) almost 2 times longer than in Group 1 children.

Evaluation of the parameters of multiplicity and duration of vomiting revealed that patients infected with EBV (Group 2) had almost 1.5 times lower daily multiplicity of vomiting, compared with uninfected (2.38 ± 1.43 and 4.21 ± 2.23 $p = 0.002$). The duration of vomiting was almost the same (1.36 ± 0.74 days and 1.17 ± 0.83 days, $p = 0.330$).

As can be seen from Table I, the maximum frequency diarrhea in children of both groups in the acute period was almost the same. However, in patients infected with EBV (Group 2) the duration of diarrhea was significantly longer than in patients with mono-RVI (Group 1) (4.52 ± 0.84 days and 3.57 ± 0.79 days, $p < 0.001$).

When studying the parameters of catarrhal syndrome, no differences were found in the frequency of their occurrence among the compared groups. This syndrome was identified in 26 patients (78.79%) in Group 1 and in 18 patients (78.26%) in Group 2, ($p = 0.335$). Also there were no differences in duration of catarrhal syndrome (rhinitis, pharyngitis), were found (3.36 ± 1.03 days and 3.60 ± 0.65 days in Group 1 and in Group 2, respectively).

The revealed clinical differences in the course of RVI on the background of EBV infection, such as lower temperature response rates and lower vomiting rate, at the onset of the disease, probably became a factor in later hospitalization of these children from the onset of the disease compared with patients in Group 1 (2.3 ± 0.8 days and 1.8 ± 0.8 days, $p = 0.05$).

Given the presence of clinical differences in RVI in the comparison groups, the study also involved an assessment of the relative and absolute content of subpopulations of T- and B-lymphocytes and immunoglobulins of classes A, M, G in the blood of children of both groups during the disease.

Table II

Indices of cellular and humoral links of the immune response in the examined patients in the acute period of the disease (M±SD)

Indices, reference norms	**Group 1 (n=33)**	**Group 2 (n=23)**	***P***

Lymphocytes, abs. (N – 4-9 *10^9/L)	5.11±1.67	5.21±1.45	0.696
CD 3^+, % (N – 50 - 80%)	60.61±6.63	60.00±7.42	0.688
CD 3^+, abs (N – 1,0 - 1,5 *10^9/L)	3.09±1.04	3.14±0.98	0.874
CD 4^+, % (N – 33 - 46%)	28.94±5.02	31.04±5.17	0.130
CD 4^+, abs (N – 0,4 – 0,8*10^9/L)	1.48±0.56	1.60±0.45	0.310
CD 8^+, % (N – 17 – 30%)	23.67±3.29	28.57±3.82	***<0.001***
CD 8^+, abs (N – 0,2 - 0,4 *10^9/L)	1.23±0.50	1.50±0.48	0.058
CD 4^+ / CD 8^+ (N – 1,4 - 2,0)	1.23±0.20	1.10±0.24	***0.001***
CD 16^+, % (N – 12 - 23%)	26.15±5.39	22.17±3.65	***0.002***
CD 16^+, abs (N – 0,1 - 0,25*10^9/L)	1.32±0.43	1.15±0.34	0.140
CD 22^+, % (N – 17 - 31%)	21.09±2.89	20.26±2.05	0.356
CD 22^+, abs (N – 0,1-0,3*10^9/L)	1.09±0.43	1.07±0.36	0.796
Ig A, g/l (N – 0,2 - 1,0 g/l)	0.42±0.11	0.43±0.10	0.500
Ig M, g/l (N – 0,19 - 1,46 g/l)	0.80±0.27	0.73±0.15	0.260
Ig G, g/l (N – 4,53 – 9,16 g/l)	7.82±0.75	8.17±0.74	0.086

As can be seen from Table II, the total number of lymphocytes (abs) and their subpopulations of $CD3^+$ (%, abs), $CD4^+$ (%, abs) in the acute period of the disease among the comparison groups had no significant differences. In contrast, Group 2 patients were found to have a significantly higher relative content of $CD8^+$ T-lymphocytes than in Group 1 patients (28.57 ± 3.82 and 23.67 ± 3.29, $p <$ ***0.001***), and the absolute content of $CD8^+$ cells tended to increase relative to children of the first group.

The immunoregulatory index (IRI) in patients infected with EBV was significantly lower than in the first group (1.10 ± 0.24 and 1.23 ± 0.20, $p =$ ***0.001***). Besides, Group 2 patients, in the acute period of the disease, were shown to have a significant decrease in the relative content of $CD16^+$ T-lymphocytes (22.17 ± 3.65 and 26.15 ± 5.39 $p =$ ***0.002***). Indices of the humoral part of the immune response did not have significant differences among children of the comparison groups at the onset of the disease.

Table III

Indices of cellular and humoral links of the immune response in the examined patients in the period of early convalescence (M ± SD)

Indices	**Group 1 (n=33)**	**Group 2 (n=23)**	***P***
Lymphocytes, abs. (N – 4-9 *10^9/L)	3.52±0.63	3.58±0.56	0.652
CD 3^+, % (N – 50 - 80%)	63.66±6.15	63.96±5.84	0.782
CD 3^+, abs (N – 1,0 - 1,5 *10^9/L)	1.97±0.86	2.30±0.47	0.194
CD 4^+, % (N – 33 - 46%)	39.38±3.09	37.83±2.67	0.081
CD 4^+, abs (N – 0,4 – 0,8*10^9/L)	1.21±0.51	1.35±0.22	0.653
CD 8^+, % (N – 17 – 30%)	29.48±3.8	34.52±3.01	***<0.001***
CD 8^+, abs (N – 0,2 - 0,4 *10^9/L)	0.91±0.38	1.24±0.24	***<0.001***
CD 4^+ / CD 8^+ (N – 1,4 - 2,0)	1.34±0.12	1.10±0.14	***<0.001***
CD 16^+, % (N – 12 - 23%)	19.9±3.88	16.65±2.44	***<0.001***
CD 16^+, abs (N – 0,1 - 0,25*10^9/L)	0.62±0.30	0.60±0.14	0.211
CD 22^+, % (N – 17 - 31%)	33.38±4.35	28.04±2.75	***<0.001***
CD 22^+, abs (N – 0,1-0,3*10^9/L)	1.03±0.44	1.00±0.19	0.104
Ig A, g/l (N – 0,2 - 1,0 g/l)	0.90±0.20	0.83±0.20	0.254
Ig M, g/l (N – 0,19 - 1,46 g/l)	1.86±0.43	1.15±0.23	***<0.001***
Ig G, g/l (N – 4,53 – 9,16 g/l)	10.34±0.84	10.71±0.94	0.063

During the period of early convalescence there were no significant differences in the absolute content of lymphocytes and $CD3^+$ (%, abs), $CD4^+$ (%, abs) and their subpopulations.

When analyzing the levels of $CD8^+$ T-lymphocytes in the blood of patients in the study groups, it was found that in patients infected with EBV, in the period of early convalescence there was a significant increase in both their relative and absolute content ($p < 0.001$).

Due to the increased level of $CD8^+$ T-cells, patients with latent EBV infection developed an imbalance causing a significant decrease in the IRI during early convalescence, compared with patients of Group 1 (1.11 ± 0.14 and 1.34 ± 0.12%, $p < 0.001$).

The relative content of $CD16^+$ T-lymphocytes during the disease remained significantly lower in patients with background EBV infection than in children without it (16.65 ± 2.44 and 19.9 ± 3.88, $p < 0.001$).

The relative level of $CD22^+$ T-cells in the period of early convalescence increased in both groups, but in children on the background of EBV infection (Group 2) there was a significantly lower relative level (28.04 ± 2.75 and 33.38 ± 4.35, $p < 0.001$). The absolute content of $CD22^+$ T-cells had no significant differences among the comparison groups. Besides, Ig M content in Group 2 children in the period of early convalescence relative to Group 1 patients was significantly lower (1.15 ± 0.23 and 1.86 ± 0.43, $p < 0.001$).

Discussion

There is significant number of scientific researches devoted to the study of effect of EBV on the immune response and course of other infectious diseases. However, we did not find the researches which study effects of EBV on RVI.

The current study demonstrates the effect of EBV on the clinical and immunological parameters of RVI. Thus, in the acute period of the disease, the presence of Epstein-Barr virus infection in children with RVI leads to their later hospitalization, lower temperature response rates, and lower frequency of vomiting in the onset of the disease. To our knowledge, such effects can reduce the risk of dehydration and contribute to effective oral rehydration in the prehospital phase, and possibly even reduce the number of hospitalizations. In the period of early convalescence in children with latent EBV infection, a longer persistence of fever and diarrhea was observed. This finding coincides with the data of other scientists who studied the effect of EBV on the course of intestinal and respiratory diseases, although these authors describe significant manifestation of clinical symptoms predominantly in acute period of the disease [14, 15].

Analysis of the interrelations of immune parameters in children infected with EBV showed significantly higher relative and absolute count of $CD8^+$ T-lymphocytes respectively during whole course of disease and in the period of convalescence. The

increase in the level of $CD8^+$ T-lymphocytes is probably due to the stimulation of $CD8^+$ cell synthesis by herpesviruses, which is described in researches [6, 16, 17]. Some authors also point to the immunomodulatory properties of $CD8^+$ T-lymphocytes, due to their ability to be activated in response to other pathogens [12]. It is possible that the activity of T-cytotoxic lymphocytes was the cause of a less pronounced clinical manifestation at the beginning of the disease. Decreased IRI, in our opinion, is due to the increased content of $CD8^+$ lymphocytes, which are directly used in the calculation of IRI. Although according to the literature, the approximation of IRI to 1.0, found in children of second group, indicated a tendency to immunodeficiency [16].

Both in the acute period and in the period of early convalescence, a reduced level of $CD16^+$ T-lymphocytes was found in children with latent EBV infection, which is probably associated with the inhibitory effect of herpesviruses on NK-cells, which was described in other studies [18, 19]. The lack of significant differences in the absolute count of $CD16^+$ T-lymphocytes necessitates further study of this issue.

In addition, the period of early convalescence in patients infected with EBV is characterized by a delay in activation of $CD22^+$ T-cells on the background of lower than in the control group content of Ig M, which may indicate a delay in activation of the humoral immune response. We hypothesize that these changes could increase the duration of fever and diarrhea in patients of second group.

The data suggest that the presence of EBV infection directly affects the mechanism of the immune response by altering the count of T-lymphocytes, especially cytotoxic, and immunoglobulins, which ultimately contributes to changes in the clinical manifestations of the disease.

Conclusions

The presence of EBV infection in patients with RVI is associated with less pronounced clinical symptoms of RVI in children in the acute period of the disease.

During the period of early convalescence -increased duration of the main symptoms of rotavirus gastroenteritis

Concerning of the cellular part of the immune system in children infected with EBV, we have not established clear criteria that would indicate the immunosuppressive effect of latent WEB infection on the immune response of the child during acute rotavirus gastroenteritis.

The period of convalescence in children infected with EBV is characterized by a lower content of CD22 + T-cells and IgM than in children without background infection. In our opinion, such differences indicate a delay in the activation of the humoral link of the immune response, and, probably, in combination with other factors, is a factor in the prolongation of clinical manifestations of RVI.

Prospects for further research. In our opinion, the clinical and immunological parameters of RVI can be used to create an algorithm for early diagnosis of EBV infection in children with rotavirus gastroenteritis, which will improve certain therapies for these patients and tactics for monitoring convalescents.

The article is part of the research work “The significance of herpes virus infection in the formation of the clinical course of gastrointestinal diseases of infectious etiology in children”, No.0120U102471

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Conflict of interest: The authors declare no conflict of interest.

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