UDC 616.98:578.823.91:578.825.11/.12]-053.2-078:612.017

M.Yu. Sliepchenko, O.M. Olkhovska, Ya.V. Kolesnyk, A.V. Gavrylov

Clinical and immunological features of rotavirus infection in children infected with herpesviruses

Kharkiv National Medical University, Ukraine

Ukrainian Journal of Perinatology and Pediatrics. 2024. 3(99): 96-103; doi: 10.15574/PP.2024.3(99).96103

For citation: Sliepchenko MYu, Olkhovska OM, Kolesnyk YaV, Gavrylov AV. (2024). Clinical and immunological features of rotavirus infection in children infected with herpesviruses. Ukrainian Journal of Perinatology and Pediatrics. 3(99): 96-103; doi: 10.15574/PP.2024.3(99).96103.

The basis for conducting the study was the absence in the scientific literature of works devoted to the study of clinical and immunological features of rotavirus infection (RVI) in children against the background of the latent form of herpesvirus infection (IHVI) caused by cytomegalovirus (CMV) and human herpesvirus type 6 (HHV-6).

The **aim** — to identify clinical and immunological features of RVI in children with IHVI caused by CMV and HHV-6 that will contribute to the early diagnosis of IHVI in patients.

Materials and methods. A total of 81 children aged 12–36 months with RVI were examined. The Group 1 included 33 children who were not found to be infected with any of the herpesviruses. The Group 2 included 17 children who were suffering from RVI against the background of IHVI caused by CMV. The Group 3 included 31 children suffering from RVI against the background of IHVI caused by HHV-6 type. Statistical processing of the results was carried out using the IBM® SPSS® 25.0 program for Microsoft® Windows®.

The results. The presence of IHVI caused by CMV in the acute period (AP) of RVI leads to lower indicators of temperature reaction, lower frequency of vomiting, a decrease in the immunoregulatory index (IRI) against the background of an increase in the level of CD8+ T-lymphocytes. In addition to lower numbers of the temperature reaction, the level of IgA was increased in children with IHVI caused by HHV-6. During the convalescent period (CP), CMV is associated with an increase in the duration of fever and diarrhea, an increased content of CD8+ T-cell counts, and lower IRI, CD16+, CD22+ T-cells, and IgM scores. In patients with IHVI caused by HHV-6, fever, diarrhea, and catarrhal syndrome persisted longer against the background of reduced levels of IRI, CD22+ T cells, and IgM.

Conclusions. IHVI is caused by CMV and HHV-6, it has different effects on clinical and immune indicators in children with RVI.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Local Ethics Committee of the institution indicated in the work. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: rotavirus infection, cytomegalovirus, human herpesvirus type 6, cellular link of the immune response, humoral link of the immune response.

Клініко-імунологічні особливості ротавірусної інфекції у дітей, інфікованих герпесвірусами

М.Ю. Слєпченко, О.М. Ольховська, Я.В. Колесник, А.В. Гаврилов

Харківський національний медичний університет, Україна

Підґрунтям для проведення дослідження стала відсутність у науковій літературі робіт, присвячених вивченню клініко-імунологічних особливостей ротавірусної інфекції (РВІ) у дітей на тлі латентної форми герпесвірусної інфекції (лГВІ), обумовленої цитомегаловірусом (ЦМВ) та вірусом герпесу людини 6 типу (ВГЛ-6).

Мета — виявити клініко-імунологічні особливості РВІ у дітей із лГВІ, обумовленою ЦМВ та ВГЧ-6, що сприятиме ранній діагностиці лГВІ у пацієнтів.

Матеріали та методи. Обстежено 81 дитину віком 12–36 місяців хвору на РВІ. 1 група — 33 дитини, у котрих не виявили інфікування жодним із вірусів групи герпесу. 2 група — 17 дітей, які переносили РВІ на тлі лГВІ, обумовленої ЦМВ. 3 група — 31 дитина, що переносила РВІ на тлі лГВІ, обумовленої ВГЛ-6 типу. Статистичну обробку результатів проведено за допомогою програми IBM® SPSS® 25.0 для Microsoft® Windows®.

Результати. Наявність лГВІ, обумовленої ЦМВ, у гострому періоді (ГП) РВІ призводить до нижчих показників температурної реакції, меншої кратності блювоти, зниженню показника імунорегуляторного індексу (ІРІ) на тлі збільшення рівня CD8+ Т-лімфоцитів. У дітей із лГВІ, обумовленою ВГЛ-6, окрім нижчих цифр температурної реакції, був підвищений рівень IgA. У період реконвалесценції (ПР) ЦМВ асоціюється зі збільшенням тривалості лихоманки та діареї, підвищеним вмістом CD8+ Т-клітин та нижчими показниками ІРІ, вмісту CD16+, CD22+ Т-клітин і IgM. У пацієнтів із лГВІ, обумовленою ВГЛ-6, довше зберігались лихоманка, діарея та катаральний синдром на тлі зниженого рівня ІРІ, CD22+ Т-клітин і IgM.

Висновки. лГВІ обумовлена ЦМВ та ВГЛ-6, по-різному впливає на клінічні та імунні показники в дітей із РВІ.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалений Локальним етичним комітетом зазначених установ. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: ротавірусна інфекція, цитомегаловірус, вірус герпесу людини 6 типу, клітинна ланка імунної відповіді, гуморальна ланка імунної відповіді.

Introduction

According to WHO data, rotavirus infection (RVI) remains one of the most frequent causes of diarrhea in young children, which leads to hospitalization [2,8]. Due to the widespread use of the vaccine for the prevention of RVI, the number of deaths has decreased, but the high incidence of rotavirus gastroenteritis prompts further research into this pathology and the search for factors that affect the course of RVI.

Another global problem of the healthcare system is herpesvirus infection, which is pantropic

and after the first infection causes lifelong latency of the virus in the host's body [3,11,14,20]. Many scientists investigate the effect of herpesviruses on the immune response and the course of other infectious and somatic diseases, but their conclusions are sometimes contradictory. Some scientists discovered the immunosuppressive effect of latent herpesvirus infection (lHVI) on the immune response of the human body and observed a worsening of the accompanying disease, while others — on the contrary, point to the immunostimulating effect of viruses of the herpes group [3,13,18]. According to some authors, slightly lower levels of CD 3+, CD 4+, CD 16+ T-cells were found in patients with viral intestinal infections occurring against the background of the latent form of infection caused by CMV than in uninfected patients [4]. However other researchers, on the contrary, indicate the increased activity of CD8+ T cells and describe the positive effect of the latent form of CMV infection on the immune response [22]. The ability of CMV to worsen and prolong the course of intestinal diseases was revealed [4,22,14].

Conclusions regarding the pathogenetic features of the HSV-6 type are also ambiguous, the study of this issue is ongoing. Some authors call this virus immunosuppressive, others — immunomodulating [24,16]. HHV-6 replicates in various types of immune cells, mainly in CD4+T cells, can multiply in monocytes, macrophages, CD3+, CD5+, CD7+ lymphocytes and natural killer cells, megakaryocytes and B-lymphocytes, changing their functional activity and quantitative content [1,13,16]. Solène Fastenackels et al. (2019) found that the response of specific T-lymphocytes to HHV-6 is less pronounced than the response of the corresponding lymphocytes to CMV. Thus, INF-γ-secreting CD4+ T-cells corresponding to HHV-6 constitute less than 0.1% of the total population of CD4+ T-cells, in contrast to CMV-specific CD4+ cells, the level of which is from 2% to 6% of the total number of T-lymphocytes [10]. Some scientists identify a connection between HHV-6 and CMV with FIRES syndrome (fever-induced refractory epileptic encephalopathy in school-aged children) and consider the long-term subfebrile syndrome as a variant of lHVI [21]. Scientists from Finland (2012), investigating the role of lHVIs in the pathogenesis of intestinal intussusception, found that in 85% of cases of intussusception, a viral infection occurred. Among all cases of intussusception, HHV-6 was detected in 45%, and CMV — in 13% of patients [15]. A team from the University of Pittsburgh (2018) studied the role of viruses in the development of different types of oncology and found that HHV-6 type was identified in 3.9% of gastric cancer and 4.7% of colon cancer samples but was not detected in any of the control samples of normal stomach or colon [7].

The analysis of modern research gives reason to believe that infection with CMV and HHV-6 type are factors that affect the body's immune response and can change the course of infectious and somatic diseases, including RVI [22,13,18,24]. The absence in the available literature of works devoted to the study of clinical and immunological features of RVI in children against the background of a latent form of lHVI caused by CMV and HHV-6 type became the basis for conducting this study. The obtained results will be the basis for early detection of latent lHVI in children with RVI and will determine the possibilities of improving the therapy of patients.

The aim — to identify clinical and immunological features of RVI in children with lHVI caused by CMV and HHV-6 that will contribute to the early diagnosis of lHVI in patients.

Materials and methods of the study

The study was conducted at the Regional Children's Infectious Clinical Hospital in Kharkiv, Ukraine, during 2017–2020. In total, 81 children aged 12 to 36 months with RVI were examined. Patients were divided into three groups: the Group 1 — 33 children suffering from rotavirus gastroenteritis without co-infection of herpesviruses; the Group 2 — 17 children suffering from RVI against the background of CMV co-infection; the Group 3 — 31 children suffering from rotavirus gastroenteritis against the background of HHV-6 type infection. When forming groups, *inclusion* (age of children from 12 to 36 months, laboratory-confirmed diagnosis of RVI, positive result for specific IgG to CMV and HHV-6 type, presence of parents' informed consent to participate in the study, lack of immunodeficiency), and *exclusion criteria* (age of children under 12 months or over 36 months, the presence of the positive result for bacterial and other viral pathogens of intestinal infections, the presence of IgM and/or IgG specific antibodies to other viruses of the herpes group, a positive result of qualitative PCR for DNA determination

of CMV and HHV-6 type, and the presence of background pathology) were used. The study groups were comparable in terms of sex, age, and disease severity.

The Group 1 included 15 (45.5%) girls and 18 (54.5%) boys; the Group 2 included 11 (64.7%) girls and 6 (35.3%) boys; the Group 3 — 16 (51.6%) girls and 15 (48.4%) boys (χ^2=1.247, p=0.526). The median age criteria in the Group 1 is 23.0 (19.0; 26.0) months, the Group 2 — 24.0 (20.5; 32.5) months, the Group 3 — 24.0 (15.0; 31.0) months, p=0.186. The moderate course of RVI was diagnosed in 15 (45.5%) children of the Group 1, 11 (64.7%) of the Group 2, and 16 (51.76%) of the Group 3. 18 (54.50%) patients of Group 1, 6 (35.3%) of the Group 2, and 15 (48.4%) of Group 3 had a severe course of RVI, χ^2=1.453, p=0.572.

The diagnosis of RVI was determined on the basis of clinical and epidemiological data and the isolation of rotavirus antigen from the feces of patients using CITO TEST ROTA-ADENO test systems (immunochromatographic method) (LLC «Pharmasco», Ukraine). The latent form of lHVI was established based on the positive results of the blood serum test at the debut of an intestinal infection for specific IgG antibodies to CMV and HHV-6 type by enzyme-linked immunosorbent assay (ELISA) («Vector-Best» Ukraine reagent kit). The presence of specific immunoglobulins of class M to CMV and HHV-6, immunoglobulins of class M and G to herpes simplex type 1, 2 and Epstein–Barr virus, as well as the presence of nucleic acid to herpesviruses of types 1, 2, 4, 5, 6, which were determined using the polymerase chain reaction (PCR) («Amplisens» reagent kit, Ukraine).

All patients in the acute period (AP) (1–3 days) and the period of early convalescence (7–10 days) along with generally accepted laboratory tests, special immunological tests were performed: studying the state of the cellular link of the immune response (levels of CD3+, CD4+, CD8+, CD16+, CD22+ in the blood, using the method of monoclonal antibodies «GRANUM», Ukraine) and the humoral link of immunity (the content of IgM, IgA, IgG in the blood serum using a two-site immunoassay (the sandwich method) («GRANUM», Ukraine). The immunoregulatory index (IRI) was calculated based on the ratio CD4+/CD8+.

Qualitative (binomial, ordinal, nominal) indicators were described in absolute and relative (percentage) values. The result was given in the form of «abs. (%)».

The comparison of the relationship of the frequency distribution of qualitative features was carried out using the calculation of Pearson's χ^2 conjugation criterion.

The nature of the distribution of quantitative traits was assessed by the visual graphical method and using the Shapiro–Wilk test of normality. Since the evaluation of the 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 the median (Me) and the lower (LQ) and upper (UQ) quartiles. The probability of differences in quantitative indicators in two unrelated groups was determined using the Mann–Whitney U-test. The critical value of p was considered to be 0.05. Statistical processing of the results was performed using the IBM SPSS 25.0® for Windows® (Trial version) application program package. There is no conflict of interest.

The clinical and paraclinical indicators of children not infected with herpes viruses (Group 1) were used as a control. Taking into account the number of comparisons, we applied the Bonferroni correction. The established confidence level «p» was divided by the number of comparisons (the Groups 1 and 2, 1 and 3, 2 and 3 — 3 comparisons = 0.05/3 = 0.017). Therefore, in this article, p-values above 0.017 are considered unreliable.

The research meets the requirements of the Declaration of Helsinki. Examinations of patients were performed with the written informed consent of the parents. The Committee on Ethics and Bioethics of the Kharkiv National Medical University (protocol No. 7 of September 11, 2018) found that the research methods comply with the current legislation of Ukraine and international ethical requirements, do not violate ethical norms in science and standards for conducting biomedical research.

Research results and discussion

In the course of the study, we analyzed the clinical manifestations of RVI in children depending on infection with various herpesviruses.

According to the data in the Table 1, no significant differences were found among the comparison groups between the indicators of the time of occurrence of fever, catarrhal phenome-

Table 1

Indicators of clinical manifestations of RVI in children of comparison groups, Me (LQ; UQ)

Indicator	Group 1 (mono-RVI) (n=33)	Group 2 (CMV) (n=17)	Group 3 (HHV-6) (n=31)	p_{1-2}	p_{1-3}	p_{2-3}
The term of onset of temperature, days	1.0 (1.0;2.0)	2.0 (1.0;2.0)	1.0 (1.0;2.0)	0.134	0.959	0.148
Maximum temperature, °C	38.9 (38.8;39.2)	38.6 (38.3; 39.0)	38.7 (38.5; 38.8)	0.004	<0.001	0.703
Duration of fever, days	4.0 (3.0; 4.5)	6.0 (5.0; 7.0)	6.0(4.5; 6.5)	<0.001	<0.001	0.479
The term of occurrence of catarrhal phenomena, days	1.0 (1.0;1.0)	1.0 (1.0;1.0)	1.0 (1.0;1.0)	0.074	0.332	0.067
Duration of catarrhal syndrome, days	3.0 (3.0;4.0)	4.0 (3.0;4.0)	4.0 (3.0;4.0)	0.234	0.004	0.377
The term of onset of vomiting, days	2.0 (1.0;2.0)	2.0 (1.0;2.0)	1.0 (1.0;2.0)	0.874	0.267	0.363
Max frequency of vomiting times/day	4.0 (3.0;5.0)	2.0 (2.0;3.5)	3.0 (2.0;4.0)	0.009	0.019	0.359
Duration of vomiting, days	1.0 (1.0;2.0)	1.0 (1.0;1.0)	1.0 (1.0;2.0)	0.099	0.932	0.148
The term of onset of diarrheal syndrome, days	2.0(1.0;2.0)	2.0 (1.0;2.0)	1.0 (1.0;2.0)	0.209	0.450	0.103
Frequency of diarrhea, times/day	5.0 (4.5;6.0)	5.0 (4.5;6.0)	6.0 (4.0;7.0)	0.717	0.560	0.415
Duration of diarrhea, days	3.0 (3.0;4.0)	5.0 (4.0;6.0)	5.0 (4.0;5.0)	<0.001	<0.001	0.544

Note: p_{1-2} — between indicators of patients of the Groups 1 and 2; p_{1-3} — between indicators of patients of the Groups 1 and 3; p_{2-3} — between indicators of patients of the Groups 2 and 3.

Table 2

Indicators of the immune response of patients in the AP of RVI, Me (LQ; UQ)

Indicator	Group 1 (mono-RVI) (n=33)	Group 2 (CMV) (n=17)	Group 3 (HHV-6) (n=31)	p_{1-2}	p_{1-3}	p_{2-3}
Lymphocytes, abs	5.2 (3.4;6.5)	5.4 (4.2;6.3)	4.9 (3.9;6.5)	0.774	0.863	0.690
CD 3+, %	59.0 (55.5;66.0)	60.0 (56.0;65.5)	62.0 (57.5;67.0)	0.951	0.142	0.305
CD 3+, ×109/l	3.2 (2.2;3.8)	3.3 (2.3;3.8)	3.2 (2.4;3.9)	0.759	0.930	0.897
CD 4+, %	28.0 (25.0;32.5)	30.0;(28.0;31.5)	30.0 (28.5;34.0)	0.289	0.043	0.463
CD 4+, ×109/l	1.5 (1.0;1.8)	1.4 (1.3;1.8)	1.6 (1.1;1.9)	0.660	0.472	0.983
CD 8+, %	24.0 (22.0;25.5)	30.0 (27.5;30.0)	26.0 (24.5;30.0)	<0.001	0.002	0.015
CD 8+, ×109/l	1.1 (0.7;1.5)	1.5 (1.2;1.8)	1.4 (0.9;1.7)	0.024	0.390	0.276
CD 4/CD 8 (IRI)	1.2 (1.0;1.3)	1.0 (0.9;1.1)	1.1 (1.0;1.2)	<0.001	0.142	0.005
CD 16+, %	25.0 (22.0;28.5)	23.0 (21.0;24.5)	25.0(22.5;29.0)	0.054	0.943	0.047
CD 16+, abs.	1.2 (1.0;1.6)	1.1 (0.9;1.4)	1.2 (0.9;1.6)	0.373	0.528	0.698
CD 22+, %	21.0 (19.0;23.0)	22.0 (19.5;26.5)	21.0 (19.0;27.0)	0.289	0.435	0.766
CD22+,×109/l	1.1 (0.7;1.3)	1.1 (1.0;1.3)	1.1 (0.8;1.3)	0.264	0.732	0.525
Ig A, g/l	0.4 (0.3;0.5)	0.3 (0.2;0.4)	0.5 (0.4;0.6)	0.290	<0.001	0.001
Ig M, g/l	0.7 (0.6;0.9)	0.7 (0.6;0.8)	0.6 (0.6;0.7)	0.966	0.068	0.061
Ig G, g/l	8.0 (7.3;8.3)	8.0 (7.1;8.8)	8.1 (7.2;8.5)	0.738	0.494	0.752

Note: p_{1-2} — between indicators of patients of the Groups 1 and 2; p_{1-3} — between indicators of patients of the Groups 1 and 3; p_{2-3} — between indicators of patients of the Groups 2 and 3.

na, vomiting and diarrhea, as well as the duration of vomiting, diarrhea and catarrhal phenomena.

It was found that in patients of the Groups 2 and 3, the maximum values of temperature reaction (p_{1-2}=0.004, p_{1-3}<0.001) were significantly lower than similar indicators in patients in the Group 1. At the same time, the duration of fever in them was significantly longer ($p_{1-2,1-3}$<0.001) in comparison with patients of the Group 1. The duration of the catarrhal syndrome during the course of the disease was longer in children of the Group 3 compared to patients who were not infected with herpesviruses (p_{1-3}=0.004). Only in the Group 2, the frequency of vomiting was significantly lower compared to patients in the Group 1 (p_{1-2}=0.009). At the same time, there were no significant differences between the comparison groups in terms of the time of onset and duration of vomiting. Diarrhea syndrome manifested itself in all patients on the 1st–2nd day of the disease; there were no differences in the frequency of defecation in uninfected and infected with different herpesviruses. At the same time, the duration of diarrhea in patients of the Groups 2 and 3 was significantly longer compared to the indicators of children who were not infected with herpes viruses ($p_{1-2,1-3}$<0.001).

The results of the immunological examination of patients in the observation groups in different periods of RVI are given in Tables 2 and 3.

Table 3

Indicators of the immune response of patients in the period of early convalescence of RVI, Me (LQ; UQ)

Indicator (%, abs×10⁹/l)	Group 1 (mono-RVI) (n=33)	Group 2 (CMV) (n=17)	Group 3 (HHV-6) (n=31)	p_{1-2}	p_{1-3}	p_{2-3}
Lymph., abs.	3.5 (2.9;3.9)	4.1 (3.4;5.3)	3.4 (2.9;4.2)	0.025	0.876	0.077
CD 3+, %	63.0 (59.0;66.0)	64.0 (61.0;66.0)	65.0 (60.0;67.0)	0.593	0.362	0.728
CD 3+, ×10⁹/l	2.1 (1.7;2.5)	2.3 (1.95;3.2)	2.1 (1.8;2.5)	0.081	0.444	0.262
CD 4+, %	40.0 (37.0;42.0)	37.0 (35.0;38.0)	38.0 (36.0;40.0)	0.036	0.208	0.213
CD 4+, ×10⁹/l	1.2 (1.1;1.5)	1.4 (1.1;1.8)	1.3 (1.0;1.4)	0.301	0.840	0.300
CD 8+, %	29.0 (27.0;32.0)	35.0 (32.0;35.0)	31.0 (29.0;32.5)	<0.001	0.142	0.001
CD 8+, ×10⁹/l	0.9 (0.8;1.1)	1.3 (1.0;1.6)	0.9 (0.8;1.2)	0.001	0.432	0.027
CD 4/CD 8	1.3 (1.2;1.4)	1.0 (1.0;1.0)	1.2 (1.1;1.3)	<0.001	0.008	<0.001
CD 16+, %	19.0 (17.0;21.0)	17.0 (16.0;18.0)	18.0 (16.0;21.0)	0.003	0.216	0.110
CD 16+, ×10⁹/l	0.6 (0.5; 0.7)	0.6 (0.5; 0.7)	0.6 (0.5;0.7)	0.601	0.936	0.531
CD 22+, %	33.0 (30.5;36.5)	30.0 (28.0;32.0)	28.0 (26.0;32.0)	0.009	<0.001	0.338
CD 22+, ×10⁹/l	1.1 (0.9; 1.2)	1.1 (0.8; 1.4)	0.9 (0.8;1.1)	0.545	0.160	0.178
Ig A, g/l	0.9 (0.7; 1.0)	0.8 (0.7; 1.0)	0.8 (0.7;0.9)	0.603	0.355	0.678
Ig M, g/l	1.9 (1.5; 2.1)	1.4 (1.2; 1.5)	1.5 (1.3;1.7)	<0.001	<0.001	0.738

Note: p_{1-2} — between indicators of patients of the Groups 1 and 2; p_{1-3} — between indicators of patients of the Groups 1 and 3; p_{2-3} — between indicators of patients of the Groups 2 and 3.

In the AP of RVI, no significant differences were found between indicators of lymphocyte content, percentage and absolute content of CD 3+, CD 4+ CD 16+, CD 22+ and absolute content of CD 8+ T cells, as well as the levels of IgM and IgG of the observation groups (Table 2). In all patients with background lHVI, the relative content of CD 8+ T-lymphocytes is significantly higher compared to children of the Group 1 (p_{1-2}<0.001, p_{1-3}=0.002). At the same time, in patients who are infected with HHV-6 type (Group 3), it was determined that the CD 8+ cell content was significantly lower in children infected with CMV (Group 2) (p_{2-3}=0.015). Significant differences were determined according to the IRI indicator in children of 2 groups: IRI was reliably low incompared to the Group 1 (p_{1-2}<0.001), as well as to the index of patients of the Group 3 (p_{2-3}=0.005) [19].

The study of the humoral link of the immune response in patients infected with HHV-6 (Group 3) revealed the highest median indicators of IgA content, which significantly prevailed over similar indicators of patients from the Groups 1 and 2 (p_{1-3}<0.001, p_{2-3}=0.001).

In the period of early convalescence, the percentage and absolute content indicators CD 3+, CD 4+, and absolute content of CD 16+, CD 22+ and levels of IgA and IgG had no significant differences among the children of the comparison groups (Table 3).

Significantly higher indicators of the relative content of CD 8+ cells were recorded in patients of the Group 2, not only in relation to the indicators of children in the Group 1 but also in comparison with the indicators of the Group 3 (p_{1-2}<0.001, p_{2-3}=0.001). The absolute content of CD 8+ lymphocyte count of children in the Group 2 was significantly higher than the CD 8+ content of patients in the Group 1 (p_{1-2}=0.001). The IRI indicators in children of the Group 2 and 3 were significantly lower than in patients of Group 1 (p_{1-2}<0.001, p_{1-3}=0.008). At the same time, the IRI levels in the patients of the Group 2 were significantly lower compared to the indicators in the children of the Group 3 (p_{2-3}<0.001). Also, in children of the Group 2, there is a decrease in the relative content of CD16+ T-lymphocytes compared to patients of the Group 1 (p_{1-2}=0.003).

In the period of early convalescence in patients with a background infection of CMV (Group 2) and HHV-6 type (Group 3), significantly lower values of the median content of CD 22+ cells (p_{1-2}=0.009 and p_{1-3}<0.001) and IgM (p_{1-2}, p_{1-3}<0.001) were established compared to the values of patients of the Group 1 (mono-RVI).

The obtained results indicate that rotavirus gastroenteritis in young children is a life-threatening infection that preserves inherent clinical symptoms and is characterized by a severe course. According to O.V. Usachova (2020), in the Zaporizhzhia region, RVI in children aged 12 to 24 months had a severe course in most (70.2%) cases, which is consistent with our data on the severity of the disease in children with RVI as a monoinfection, although the percentage was somewhat lower (54.50%) [8,23]. Presumably, this difference is due

to age differences — it is known that intestinal infections are more severe in children under one year, and our study included children aged 12 to 36 months. In addition to the diarrheal syndrome, the presence of vomiting in children is typical, which according to our data developed during the first two days, the frequency was 2–4 times a day, and against the background of the treatment, it disappeared within 1–2 days.

Our research shows that the presence of lHVI (CMV, HHV-6 type) contributes to the prolongation of the persistence of fever and diarrheal syndrome in children with RVI, as indicated by other scientists who studied infectious lesions of the intestine [4,14]. It was determined that with bacterial lesions of the intestine, the presence of concomitant CMV infection leads to the prolongation of both local symptoms from the intestine and the general intoxication syndrome, which leads to a longer stay of patients in the hospital [6,17]. Assessment of clinical manifestations of RVI shows that CMV and HHV-6 type have almost the same effect on clinical symptoms in young children, but only in children infected with HHV-6, we observed a longer persistence of catarrhal manifestations (p_{1-4}=0.004). In our opinion, this is due to the fact that the lymphoid tissue of the oropharynx belongs to one of the main zones of persistence of the HHV-6 type, which can be stored for a long time [13].The results obtained by us partially coincide with the data of other scientists who studied the effect of herpesviruses on the course of bacterial diarrhea [4–6].

At the same time, in patients with concomitant CMV infection lower levels of temperature response have been established, as well as a significantly lower frequency of vomiting was recorded (p_{1-3}=0.009) compared with patients with RVI without co-infection. Such results differ from those obtained when studying the effect of herpesviruses on the course of Escherichiosis and Shigelosis in children [6,17]. In our opinion, this is due to the fact that the first symptom of bacterial diarrhea is a symptom of general intoxication, one of the manifestations of which is fever and vomiting, as well as the fact that the study was conducted in older children.

The results of determining the indicators of the immune response mostly coincide with the data of the specialized literature regarding the influence of β-group herpesviruses on the immune response of children with infectious diseases of the gastrointestinal tract. Changes in both the cellular and humoral links of the immune response were found in young children with RVI.

The course of RVI in children with concomitant lHVI occurs against the background of significantly higher levels of cytotoxic CD 8+ lymphocytes in the blood. At the same time, in patients infected with CMV, the level of CD 8+ cells significantly exceeds the indicators not only in children with RVI as a monoinfection, but also in children infected by HHV-6 type. In our opinion, it is associated with a higher ability of CMV to stimulate specific cytotoxic T-cells compared to HHV-6 type [1,10,12]. The obtained results differ from studies of the immune response in children with Shigellosis infected with CMV, which may be due to transient immunosuppression in severe bacterial gastroenterocolitis in children [5]. In the period of early convalescence of RVI, in children with concomitant CMV infection, significantly higher indicators of the relative content of CD 8+ lymphocytes are preserved against the background of a lower level of IRI compared to children infected with HHV-6 type, which is consistent with the data of some researchers [1].

The reduced percentage levels of CD 16+ T-lymphocytes found by us in children with RVI on the background of CMV are probably related to the suppressive effect of CMV on natural killers, as determined by other authors [9].

A significant decrease in the IRI indicator in children infected with CMV, on the one hand, may be associated with an increased content of CD 8+ cells, the level of which is directly used for its calculation, and on the other hand, it may indicate the immunosuppressive effect of CMV on the child's immune system [14].

The study of the humoral link of the immune response revealed a significant effect of CMV on immune reactivity. It is in these patients that we determined significantly lower levels of IgA, which may be the result of the suppressive effect of this virus on the immune response. In the period of early convalescence, the course of RVI in patients with concomitant latent infection caused by CMV and HHV-6 type occurs against the background of significantly lower levels of the median content of CD 22+ cells and IgM. The latter fact may indicate a delay in the activation of the humoral link of the immune response and may be one of the factors in the prolongation of the clinical manifestations of RVI in children with coinfection.

Therefore, the presence of lHVI in children affects the frequency of detection of certain symptoms of rotavirus gastroenteritis and contributes to the prolongation of these symptoms, which is probably due to the influence of CMV and HHV-6 type on the child's immune response.

Conclusions

At the current stage, RVI in young children retains its characteristic main clinical signs.

The presence in children with RVI, a concomitant CMV or HHV-6 type infection affects the clinical symptoms of RVI: there is a prolongation of the fever duration, diarrhea and catarrhal syndrome against the background of a lower frequency of vomiting and a lower temperature reaction in the AP of RVI.

The latent form of CMV or HHV-6 type infection affects the indicators of the immune response of children with RVI. In the AP, there is an increase in indicators of cytotoxic CD 8+ lymphocytes. In the period of early convalescence, patients with RVI and a latent form of CMV or HHV-6 type experience a delay in the response of the humoral link of immunity, which is evidenced by lower levels of the median content of CD 22+ cells and IgM compared to children with mono-RVI.

The presence of lHVI in children with RVI affects the clinical course of intestinal infection and the immunological indicators of patients, and the most significant changes observed in children with latent CMV infection. This probably indicates different mechanisms of interaction of viruses with the human body, despite the fact that CMV and HHV-6 types belong to the same group of herpes.

Prospects for further research. The results of the study can be used to develop a mathematical model for predicting the presence of CMV and/or HHV-6 type infections in children with rotavirus gastroenteritis, which will make it possible to predict the course of RVI.

No conflict of interests was declared by the authors.

References/Література

1. Asouri M, Sahraian M, Karimpoor M, Fattahi S, Motamed N, Doosti R et al. (2020). Molecular Detection of Epstein–Barr Virus, Human Herpes Virus 6, Cytomegalovirus, and Hepatitis B Virus in Patients with Multiple Sclerosis. Middle East journal of digestive diseases, 12(3): 171–177. https://doi.org/10.34172/mejdd.2020.179.
2. Badur S, Öztürk S, Pereira P, AbdelGhany M, Khalaf M, Lagoubi Y et al. (2019). Systematic review of the rotavirus infection burden in the WHO-EMRO region. Human vaccines & immunotherapeutics. 15(11): 2754–2768. https://doi.org/10.1080/21645515.2019.1603984.
3. Bowyer G, Sharpe H, Venkatraman N, Ndiaye PB, Wade D, Brenner N et al. (2020). Reduced Ebola vaccine responses in CMV+ young adults is associated with expansion of CD57+KLRG1+ T cells. The Journal of experimental medicine. 217(7): e20200004. https://doi.org/10.1084/jem.20200004.
4. Bukiy S. (2021). Humoral immune response of children with Shigellosis and infected with Cytomegalovirus. Experimental and Clinical Medicine. 85(4): 62–66. [Букій С. (2021). Гуморальна імунна відповідь дітей, хворих на шигельоз та інфікованих цитомегаловірусом. Експериментальна і клінічна медицина. 85(4): 62–66]. https://doi.org/10.35339/ekm.2019.85.04.09.
5. Bukiy SM, Olkhovska OM. (2020). Dynamics of cellular immune response in Shigellosis in children infected with Cytomegalovirus. World Science. 2; 3(55): 4–7. https://doi.org/10.31435/rsglobal_ws/31032020/6973.
6. Bukij S, Olkhovskaya O. (2020). Clinical and paraclinical features of the course of shigellosis in children infected with cytomegalovirus. Experimental and Clinical Medicine. 82(1): 75–80. [Букій С, Ольховська О. (2020). Клініко-параклінічні особливості перебігу шигельозу у дітей, інфікованих цитомегаловірусом. Експериментальна і клінічна медицина. 82(1): 75–80]. https://doi.org/10.35339/ekm.2019.01.11.
7. Cantalupo PG, Katz JP, Pipas JM. (2018). Viral sequences in human cancer. Virology. 513: 208–216. https://doi.org/10.1016/j.virol.2017.10.017.
8. Crawford SE, Ramani S, Tate JE, Parashar UD, Svensson L, Hagbom M et al. (2017). Rotavirus infection. Nature reviews. Disease primers. 3: 17083. https://doi.org/10.1038/nrdp.2017.83.
9. De Pelsmaeker S, Romero N, Vitale M, Favoreel HW. (2018). Herpesvirus Evasion of Natural Killer Cells. Journal of virology. 92(11): e02105–17. https://doi.org/10.1128/JVI.02105-17.
10. Fastenackels S, Bayard C, Larsen M, Magnier P, Bonnafous P, Seddiki N et al. (2019). Phenotypic and Functional Differences between Human Herpesvirus 6- and Human Cytomegalovirus-Specific T Cells. Journal of virology. 93(13): e02321–18. https://doi.org/10.1128/JVI.02321-18.
11. Furman D, Jojic V, Sharma S, Shen–Orr SS, Angel CJ, Onengut–Gumuscu S et al. (2015). Cytomegalovirus infection enhances the immune response to influenza. Science translational medicine. 7(281): 281ra43. https://doi.org/10.1126/scitranslmed.aaa2293.
12. Hanley PJ, Bollard CM. (2014). Controlling cytomegalovirus: helping the immune system take the lead. Viruses. 6(6): 2242–2258. https://doi.org/10.3390/v6062242.
13. Hanson DJ, Tsvetkova O, Rerolle GF, Greninger AL, Sette A, Jing L et al. (2019). Genome-Wide Approach to the CD4 T-Cell Response to Human Herpesvirus 6B. Journal

of virology. 93(14): e00321–19. https://doi.org/10.1128/JVI.00321-19.
14. Jain S, Namdeo D, Sahu P, Kedia S, Sahni P, Das P et al. (2021). High mucosal cytomegalovirus DNA helps predict adverse short-term outcome in acute severe ulcerative colitis. Intestinal research. 19(4): 438–447. https://doi.org/10.5217/ir.2020.00055.
15. Lappalainen S, Ylitalo S, Arola A, Halkosalo A, Räsänen S, Vesikari T. (2012). Simultaneous presence of human herpesvirus 6 and adenovirus infections in intestinal intussusception of young children. Acta paediatrica (Oslo, Norway : 1992). 101(6): 663–670. https://doi.org/10.1111/j.1651-2227.2012.02616.x.
16. Martin LK, Hollaus A, Stahuber A, Hübener C, Fraccaroli A, Tischer J et al. (2018). Cross-sectional analysis of CD8 T cell immunity to human herpesvirus 6B. PLoS pathogens. 14(4): e1006991. https://doi.org/10.1371/journal.ppat.1006991.
17. Olkhovskyi Y, Kuznetsov S. (2020). Clinical, laboratory and instrumental features of escherichiosis in children infected by Epstein–Barr virus. Experimental and Clinical Medicine. 73(4): 73–77. [Ольховський Є, Кузнєцов С. (2020). Особливості клінічного перебігу ешерихіозу у дітей, інфікованих вірусом Епштейна–Барр. Експериментальна і клінічна медицина. 73(4): 73–77]. URL: https://ecm.knmu.edu.ua/article/view/589.
18. Schenkel JM, Fraser KA, Beura LK, Pauken KE, Vezys V, Masopust D. (2014). T cell memory. Resident memory CD8 T cells trigger protective innate and adaptive immune responses. Science (New York, N.Y.). 346(6205): 98–101. https://doi.org/10.1126/science.1254536.
19. Sliepchenko MY, Kuznetsov SV. (2021). The effect of cytomegalovirus on clinical and paraclinical as well as immune parameters of children with rotavirus infection. Pathologia. 18(2): 211–217. [Слєпченко МЮ, Кузнєцов СВ. (2021). Вплив цитомегаловірусу на клініко-параклінічні та імунні параметри дітей, які хворі на ротавірусну інфекцію. Патологія. 18(2): 211–217]. https://doi.org/10.14739/2310-1237.2021.2.230336.
20. Smith C, Moraka NO, Ibrahim M, Moyo S, Mayondi G, Kammerer B et al. (2020). Human Immunodeficiency Virus Exposure but Not Early Cytomegalovirus Infection Is Associated With Increased Hospitalization and Decreased Memory T-Cell Responses to Tetanus Vaccine. The Journal of infectious diseases. 221(7): 1167–1175. https://doi.org/10.1093/infdis/jiz590.
21. Torreggiani S, Filocamo G, Esposito S. (2016). Recurrent Fever in Children. International journal of molecular sciences. 17(4): 448. https://doi.org/10.3390/ijms17040448.
22. Usachova O, Pakholchuk T, Silina E, Matveeva T, Shulga O, Pechugina V. (2013). Peculiarities of the course of rotavirus infection in young children with cytomegaly and approaches to pathogenetic therapy. Sovremennaya pediatriya. (1): 134–138. [Усачова О, Пахольчук Т, Сіліна Є, Матвеєва Т, Шульга О, Печугина В. (2013). Особливості перебігу ротавірусної інфекції у дітей раннього віку з цитомегалією та підходи до патогенетичної терапії. Современная педиатрия. (1): 134–138].
23. Vorobyova N, Usachova O, Matveeva T. (2020). Modern clinical and laboratory features of the course of rotavirus infection in young children in the Zaporizhzhia region. Modern pediatrics. Ukraine. 4(108): 45–52. [Воробйова Н, Усачова О, Матвєєва Т. (2020). Сучасні клініко-лабораторні особливості перебігу ротавірусної інфекції у дітей раннього віку в Запорізькій області. Сучасна педіатрія. Україна. 4(108): 45–52]. doi: 10.15574/SP.2020.108.45.
24. Wang F, Chi J, Peng G, Zhou F, Wang J, Li L et al. (2014). Development of virus-specific CD4+ and CD8+ regulatory T cells induced by human herpesvirus 6 infection. Journal of virology, 88(2). 1011–1024. https://doi.org/10.1128/JVI.02586-13.

Відомості про авторів:
Слєпченко Маргарита Юріївна — д.філософ., асистентка каф. дитячих інфекційних хвороб ХНМУ. Адреса: м. Харків, пр. Науки, 4. https://orcid.org/0000-0001-5539-2177.
Ольховська Ольга Миколаївна — д.мед.н., проф., зав. каф. дитячих інфекційних хвороб ХНМУ. Адреса: м. Харків, пр. Науки, 4. https://orcid.org/0000-0002-1549-853X.
Колесник Яна Володимирівна — д.філософ., доц. каф. дитячих інфекційних хвороб ХНМУ. Адреса: м. Харків, пр. Науки, 4. https://orcid.org/0000-0003-2984-6563.
Гаврилов Анатолій Вікторович — к.мед.н., доц. каф. дитячих інфекційних хвороб ХНМУ. Адреса: м. Харків, пр. Науки. https://orcid.org/0000-0003-3926-3396.
Стаття надійшла до редакції 22.05.2024 р.; прийнята до друку 04.09.2024 р.