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CLINICAL AND LABORATORY PREDICTORS OF LATENT HERPESVIRUS INFECTION IN CHILDREN WITH ROTAVIRUS GASTROENTERITIS

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ABSTRACT

To achieve the aim there has been examined 104 children aged 1–3 years with moderate and severe forms of intestinal infection of rotavirus etiology, for which they received appropriate treatment in Kharkiv Regional Children's Infectious Diseases Clinical Hospital. Patients were divided into 2 groups: 1 group — 33 children with no concomitant herpesvirus, and 2 groups — 71 patients with rotavirus gastroenteritis and latent herpesvirus infection, caused by cytomegalovirus, Epstein-Barr virus or human herpes virus 6. Children in examined groups were comparable by gender, age, severity of main disease and other parameters.

Prognosis of latent herpesvirus infection was made by means of multiple binomial regression. Independent predictors of concomitant herpesvirus infection included maximal daily number of vomiting, maximal increase of body temperature, time of onset of catarrhal symptoms since beginning of disease, level of ketone bodies in urine, amount of leukocytes, rod-shaped neutrophils and eosinophils in common blood count during acute phase of disease. As a reference group, we used respective clinical and paraclinical indices of patients with rotavirus infection only. Accuracy of model is 81.73%.

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Aim of study was to make a mathematic model of prognosis of presence of latent herpesvirus infection in children with acute rotavirus gastroenteritis using clinical and paraclinical predictors.

Introduction. According to the World Health Organization, rotavirus infection (RVI) remains one of the leading causes of gastrointestinal diseases in children of younger age [3]. There is a large number of publications in the available literature devoted to the study of various aspects of rotavirus infection in children [5, 6]. During last decade a numerous researches devoted to influence of herpesvirus infection on clinical and laboratory parameters of infectious diseases in children have been presented [1, 2, 9]. Several authors found differences in the clinical picture and in the results of paraclinical examination of children with intestinal infections in the presence of concomitant herpesvirus infection [2, 7]. According to these scientists, concomitant herpesvirus infection complicates the course of intestinal infection, contributes to the prolongation of its clinical symptoms, and is associated with increased monocytes count on a background of reduced neutrophils count in the peripheral blood [2, 8, 10].

The various methods of diagnosing of herpes infection available to a practitioner are quite informative but costly. That is why various researchers are looking for new, cost-effective ways to detect co-infection with herpes viruses. The literature describes a method for diagnosing the presence of intracellular agents, including herpesviruses, by detecting not only specific markers by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR), but also due to the immune response of patients. The method consists in determining the levels of pro- and anti-inflammatory cytokines (IL-1β, IL-4, IL-6, TNF-α, γ-interferon and lysozyme) in the blood of children [4].

Nevertheless, this method requires the determination of cytokine content, which requires additional venous blood sampling and entails additional financial costs. The above indicates the need to develop easy-to-perform, cost-effective and accurate methods for diagnosing herpes virus infection in children.

Materials and methods. To achieve this goal, 104 children aged one to three years, with moderate and severe intestinal infections of rotavirus etiology were examined, for which they received appropriate treatment at the Regional Children's Infectious Hospital in Kharkiv. Patients were divided into 2 groups: 1st group included 33 children who did not have herpesvirus co-infection and 2nd group included 71 children with concomitant course of RVI and latent herpes infection. In second group 17 patients had RVI on the background of cytomegalovirus (CMV) infection, 23 children with Epstein-Barr virus (EBV) and 31 patients with herpes virus type 6 (HHV). Children in these groups were comparable by gender, age, severity of the disease and other parameters. 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.

Verification of the diagnosis of RVI 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 herpes virus infection was set in the presence of appropriate IgG antibodies in the serum of children and in the absence of IgM (ELISA) and nucleic acid (PCR) of 1, 2, 4, 5 and 6 types herpes viruses. The cohort of the study included children only with latent CMV, EBV, HHV6 infection.

Statistical analysis. Determining the associations of indicators with the binomial dependent variable was performed using multiple logistic regression analysis with the calculation of coefficients β, standardized coefficients β (odds ratio) and their 95% confidence intervals (CI). Maximal likelihood method of was used to include or exclude variables in stepwise analysis. A multiple binomial regression equation was developed for the model to calculate the probability of occurrence of the desired event as a percentage. The threshold value of the level of significance in the work was taken as 0.05 (p = 0.05) with the exact value of the level of significance "p" with three decimal places. The following software was used to maintain the data bank and perform the above calculations: database maintenance in the Microsoft Excel 2013 software package and statistical calculations in the IBM SPSS 25.0 software package for Windows.

Results. In order to find independent predictors of mono-RVI and concomitant RVI and herpesvirus infection, regression analysis was performed. The analysis included clinical and paraclinical parameters, including age of patients, time of onset and maximum indicators of the main symptoms of RVI, the results of clinical analysis of blood of the acute period (AP) of the disease, as well as the level of ketone bodies. The stepwise exclusion method with the maximum likelihood identified only the most reliable indicators, which turned out to be independent predictors of latent herpesvirus infection (table 1).

Table 1. Independent predictors of presence of concomitant herpesvirus infection in examined patients

Indices	**Odds ratio**	**95 % CI for OR**		**p**
		Lower	**Upper**	
Maximal daily number of vomiting	0,382	0,201	0,729	0,003
Maximal increase in body temperature, ° C	0,027	0,003	0,246	0,001
Time of onset of catarrhal symptoms since the beginning of disease, days	22,252	0,828	598,022	0,065
Urine ketone bodies, "+"	3,577	1,668	7,671	0,001
Leukocytes of AP, 10^9/L	0,488	0,308	0,773	0,002
Rod-shaped neutrophils of AP, %	3,794	1,115	12,904	0,033
Eosinophils of AP, %	3,195	1,054	9,683	0,040
Constant	1,678			0,007

According to the data provided in table 1, the maximum daily frequency of vomiting and the maximum increase in body temperature, significantly affected the likelihood of herpesvirus infection: respectively, OR = 0.382 [95 % CI 0.201–0.729], p = 0.003 and OR = 0.027 [95 % CI 0.003–0.246], p = 0.01. Thus, the increase in the patient's body temperature was significantly associated with an

increase in the odds of having a herpesvirus infection by 97.3%, and an increase in the maximum daily frequency of vomiting — by 61.8%.

At the same time, the analysis included in the model an indicator of the duration of catarrhal symptoms since the clinical manifestation of the disease: OR = 22,252 [95 % CI 0,828–598,022], p = 0,065. Although this predictor significantly increased the chances of herpesvirus infection, its value was determined at the limit of set significance level.

The number of ketone bodies in the urine was determined as a significant predictor of concomitant herpesvirus infection (OR = 3,577 [95 % CI 1,668–7,671], p = 0.001). Thus, an increase in the number of ketone bodies in the urine by one "+" was associated with a 3.5-fold increase in the odds of presence of concomitant herpesvirus infection.

Three variables of common blood count were included, which were determined as significant independent predictors of latent herpesvirus infection. Thus, the increase in leukocytes was associated with a half-less probability of infection with herpes viruses: OR = 0.488 [95 % CI 0.308–0.773], p = 0.002. Noteworthy, the neutrophil count significantly (p = 0.033) increased the odds of having a herpesvirus infection in patients with RVI in almost 4 times: OR = 3.794 [95 % CI 1.115–12.904]. The increase in the number of eosinophils in the examined patients was also associated with an increase in the odds of having a latent herpesvirus infection in 3 times: OR = 3.195 [95 % CI 1.054–9.683], p = 0.040 (table 1).

Probability (P) of presence of concomitant herpesvirus infection in patient is calculated by formula:

$$\mathrm{P} = \frac{exp^{Y}}{1 + exp^{Y}}$$

There *exp* is exponent (constant ≈ 2,718) and *Y* — is a regression equation result, which is calculated in this case by subsequent formula:

$$Y = 139{,}83 - 0{,}961 \times [\text{Max. daily vomiting}] - 3{,}599 \times [\text{Max. body temp., °C}] + 3{,}102 \times [\text{Onset of catarrhal symptoms since disease beginning, days}] + 1{,}275 \times [\text{Urine ketone bodies,"+"}] - 0{,}718 \times [\text{Leukocytes of AP, } 10^9/\text{L}] + 1{,}333 \times [\text{Rod-shaped neutrophils of AP, \%}] + 1{,}162 \times [\text{Eosinophils of AP, \%}].$$

Approbation of model was performed in patients hospitalized to Kharkiv Regional Children's Infectious Hospital, who were not included in study cohort.

Example: Danilo K. 20 months, was admitted to the hospital on the second day of illness with complaints of fever up to 38.3 ° C, weakness, decreased appetite, moderate nasopharyngitis, vomiting 3 times and loose stools 5 times. The boy became acutely ill when the above complaints appeared in the morning. In the admission department, the patient's condition was estimated of moderate severity. Objectively: the child is lethargic; skin is pale and clean. Visible mucous membranes are pale pink, the tongue is covered with a white plaque. Cries with tears. The mucous membrane of the oral cavity is moderately hyperemic. Nose respiration was somewhat difficult with moderate mucous secretions. The abdomen is bloated, rumbling, during palpation the child is worried. Preliminary diagnosis: Acute gastroenteritis of moderate severity. Mild nasopharyngitis.

Therapy: diet, oral rehydration, sorbents, biologics, antipyretics, salt drops.

Examination of fecal masses by ELISA revealed rotavirus antigen. Bacteriological examination of feces — pathogens were not detected. In urine, the number of ketone bodies was "++".

On the second day of the child's stay in the hospital laboratory study was performed: common blood count: RBC — 4.2×10^{12}/L, HGB — 136 g/L, WBC — 7.3×10^9/L, eosinophils — 1 %, rod-shaped neutrophils — 1 %, segmented neutrophils — 23 %, lymphocytes — 58 %, monocytes — 17 %, ESR — 15 mm/h. The obtained results are included in the formula

$$\mathrm{P} = \frac{exp^{(139.83 - 0.961 \times [3] - 3.599 \times [38.3] + 3.102 \times [1] + 1.275 \times [2] - 0.718 \times [7.3] + 1.333 \times [1] + 1.162 \times [1])}}{1 + exp^{(139.83 - 0.961 \times [3] - 3.599 \times [38.3] + 3.102 \times [1] + 1.275 \times [2] - 0.718 \times [7.3] + 1.333 \times [1] + 1.162 \times [1])}} =$$

$$= \frac{exp^{2.0109}}{1 + exp^{2.0109}} = \frac{7.4700}{1 + 7.4700} = 0.8819.$$

To determine the probability of a patient having a concomitant herpesvirus infection in percentage, it is needed to multiply the obtained number (P) by 100.00 % = 0.8819 × 100.00 % = 88.19 %.

Based on the results, it was concluded that the presence of herpes virus infection in this child is 88.19%. The presence of infection with one of the viruses of the herpes group was confirmed in a blood test for DNA (PCR) and IgM and IgG (ELISA) for herpes viruses types 1, 2, 4, 5 and 6. IgG to EBV (VCA) was detected in serum. Other indicators were negative.

Conclusions: Thus, the study showed a model for predicting the presence of herpes virus infection (EBV, CMV and HHV6) in children with RVI. The sensitivity of this model to the detection of mixed herpesvirus infection is 98.60 % and specificity — 45.45 %. The accuracy of the prognostic model is 81.73 %.

Prospects for further research. Prospects for further research include increasing the sample of patients, identifying and including additional anamnesis, clinical course and laboratory parameters in order to improve the specificity of the developed model.

Conflict of interest. The authors do not declare a conflict of interest.

REFERENCES

1. L.M. Boyarska, O.V. Usachova, T.S. Gerasimchuk et al (2014). Kliniko-Imunologichni osoblivosti perebigu gostrih respiratornih Infektsiy u ditey rannogo viku, infikovanih tsitomegalovirusom. *Sovremennaya pediatriya*. 1 (57), 87-91.
2. Babik R.K. (2013). Kliniko-immunologicheskie osobennosti virusnyih kishechnyih infektsiy u detey. Extended abstract of Doctor's thesis. Retrieved from http://medical-diss.com/medicina/kliniko-immunologicheskie-osobennosti-virusnyh-kishechnyh-infektsiy-u-detey
3. Selim Badur, Serdar Öztürk, Priya Pereira, et al. (2019) Systematic review of the rotavirus infection burden in the WHO-EMRO region. *Human Vaccines & Immunotherapeutics*, 15:11, 2754-2768, DOI: 10.1080/21645515.2019.1603984
4. Z.V. Eloeva, S. O. Matvienko, M. S. Dyachenko (2017). Diagnosticheskoe i prognosticheskoe znachenie vnutrikletochnyih vozbuditeley pri atipichnoy infektsionnoy patologii u detey. *Problemi bezperervnoyi medichnoyi osviti ta nauki*. 1, 21-26. Retrieved from http://www.irbis-nbuv.gov.ua/cgi-bin/irbis_nbuv/cgiirbis_64.exe?I21DBN=LINK&P21DBN=UJRN&Z21ID=&S21REF=10&S21CNR=20&S21STN=1&S21FMT=ASP_meta&C21COM=S&2_S21P03=FILA=&2_S21STR=Psmno_2017_1_6
5. S.G. Gorbunov, L.N. Mazankova, I.D. Maykova et al. (2018). Features of the immune response and the efficacy of immunotherapy for Rotavirus infection in children. *Detskie Infektsii*, 17 (3):38-46. doi.org/10.22627/2072-8107-2018-17-3-38-46
6. V.G. Maydannik, K.O. Smeyan-Gorbunova (2015). Osobennosti kletochnogo zvena immuniteta u detey, bolnyih mono-i mikst-variantami rotavirusnoy infektsii. *Zdorove rebenka*. 2 (61), 15-18.
7. E.S. Olhovskiy, S. V. Kuznetsov (2016). Osoblivosti klinichnogo perebigu esherihiozu u ditey, Infikovanih virusom Epshteyna-Barr. *Eksperementalna i klinichna meditsina*. 4 (73), 73-77. Retrieved from http://nbuv.gov.ua/UJRN/eikm_2016_4_17
8. Long HM, Meckiff BJ, Taylor GS et al. (2019). The T-cell Response to Epstein-Barr Virus–New Tricks from an Old Dog. *Front. Immunol.* Vol.10:2193. doi: 10.3389/fimmu.2019.02193
9. Vigovska O.V. (2019) Gerpesvirusni infekciyi u ditej: klasifikaciya, klinichni formi, proyavi, socialno-medichni aspekti. *Dityachij likar.* 4(49):41-51. Retrieved from https://d-l.com.ua/ua/archive/2016/4%2849%29/pages-41-51/gerpesvirusni-infekciyi-u-ditey-klasifikaciya-klinichni-formi-proyavi-socialno-medichni-aspekti
10. Usachova, O. V., Paholchuk, T. M., Silina, E. A., et al (2013). Osoblivosti perebigu rotavirusnoyi Infektsiyi u ditey rannogo viku z tsitomegalieyu ta pidhodi do patogenetichnoyi terapiyi. *Sovremennaya pediatriya*, (1), 134-138.