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PRACA ORYGINALNA
ORIGINAL ARTICLE

OPTIMIZATION OF THE TREATMENT OF ROTAVIRUS INFECTION IN CHILDREN BY USING *BACILLUS CLAUSII*

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ABSTRACT

Introduction: Rotavirus infection is a leading place in the structure of acute intestinal infections in children. Rotavirus is excreted in 40–60 % of children hospitalized with gastroenteritis all over the world. Every year, 2 million patients are hospitalized with a severe form of RVI, 25 million need medical help from a doctor and 111 million cases are treated at home.

The aim: The purpose of our study was to optimize the treatment of rotavirus infection in children by using *Bacillus clausii*.

Materials and methods: There were 65 children with a rotavirus infection under supervision. The control group was consisted of 28 practically healthy children. The study of humoral immunity was carried out on the basis of determining the serum content of immunoglobulin G, immunoglobulin M, immunoglobulin A, and secretory immunoglobulin A in coprofiltrate. In the process of treatment, the children were divided into two groups: the first received standard treatment, the second group were added to standard treatment with a probiotic drug (*Bacillus clausii*).

Results: In children with RVI with modified treatment main symptoms were reduced compared with the children receiving standard treatment, ($p < 0.001$). In patients with rotavirus infection in the acute period of the disease, a decrease in the concentration of IgA ($p < 0.001$) and an increase in IgM ($p < 0.001$) in serum and a decrease in sIgA ($p < 0.001$) in coprofiltrate was observed in comparison with children in control group. In the period of reconvalescence in children after the traditional treatment, it wasn`t revealed normalization of the immunoglobulins. Patients receiving a probiotic drug in addition to traditional treatment it was revealed normalization of the parameters of serum immunoglobulins A, M, G and sIgA in coprofiltrate.

Conclusions: So, the probiotic drug containing *Bacillus clausii* has a positive effect on the humoral immune system in children with rotavirus infection.

KEY WORDS: rotavirus, humoral immunity, children, IgA, sIgA, IgM, IgG

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INTRODUCTION

Rotavirus infection (RVI) is an urgent problem, because it is extremely widespread, especially among young children, is characterized by the severity of the course and the frequency of adverse outcomes and consequences [1]. Rotavirus infection is a leading place in the structure of acute intestinal infections in children [2]. Rotavirus is excreted in 40–60 % of children hospitalized with gastroenteritis all over the world. Every year, 2 million patients are hospitalized with a severe form of RVI, 25 million need medical help from a doctor and 111 million cases are treated at home [3, 4]. The most severe illness occurs in children at the age of 4-36 months life. Annually, rotavirus infection causes more than 600,000 deaths in children under the age of 5 who die from severe dehydration and electrolyte imbalance [5, 6]. Almost every young child is infected with rotavirus regardless of place of residence and socio-economic status [7].

Infection of the intestine with rotavirus depends on many factors: such as pH of the gastric juice, the presence of trypsin in the secretion of the duodenum, the level of secretory IgA and the features of the morphology of the mucous membrane. The virus is tropical to the cells of the cylindrical epithelium, located on the villi of the duodenum and in the upper parts of the small intestine [8]. Protection of the human body from the rotavirus is ensured by the components of cellular and humoral immunity [9]. Antibodies protect not only from the development of clinical manifestations of RVI, but also from infection. This protection depends on the level of antibodies: high-titers children are completely protected from rotavirus infection [10, 11]. These facts determine the need for effective therapeutic and prophylactic measures against rotavirus gastroenteritis.

THE AIM

The purpose of our study was to optimize the treatment of rotavirus infection in children by using *Bacillus clausii*.

MATERIALS AND METHODS

Under observation, there were 65 children with RVI from 6 months to 5 years old (main group) who were treated at

the Communal Nonprofit Enterprise "Children's Clinical Hospital of St. Zinaida" of Sumy City Council.

All children were enrolled in the study after informed consent from their parents or guardians. Ethical approval was obtained from Institutional research ethics committees.

Criteria for inclusion:

- age from 6 months to 5 years;
- rotavirus infection;
- hospitalization in acute phase of the disease;
- informed consent from children's parents or guardians;
- the absence of comorbidity in patients;
- children didn't take drugs, which were contributed to the change in the amount of trace elements.

Criteria for exclusion:

- age less than 6 months, or more than 5 years;
- Acute intestinal infection of another viral or bacterial etiology, as well as mixed variants of rotavirus infection (with other viruses or bacteria).
- hospitalization in mild phase of the disease;
- parents or guardians of children didn't give informed consent;
- presence of comorbidity in children.

Diagnosis of acute intestinal infection of rotavirus etiology was verified according to anamnesis, parent complaints, subjective and objective symptoms, and the results of the immuno-chromatographic test «CITO TEST ROTA» by Pharmaco Ltd. The control group consisted of 28 practically healthy children. The study was conducted during the acute period of the disease (for 1-2 days) and during the reconvalescence period (5-6 days). During the study, the children of the main group were divided into two groups: the I group consisted of 34 children with RVI who received standard treatment (symptomatic therapy, sorbents, rehydration therapy), and the second group included 31 children with RVI who had received standard treatment A probiotic drug containing spores of the polysaccharide strain *Bacillus clausii* - 2 × 109 and purified water (1 vial 1 time per day) is added. The study of humoral immunity was based on the determination of the content of immunoglobulin G (Ig G), immunoglobulin M (Ig M) and immunoglobulin A (Ig A) by the method of radial immunodiffusion in agar for Mancini G [12]. The level of secretory immunoglobulin A (sIg A) was determined in the excrements by the immune enzyme with the method using the «Vector Best» test systems (Novosibirsk, Russia). Statistical processing of the data was carried out by generally accepted methods of variation statistics. The following indicators were determined: arithmetic average (M), average error (m), level of differences between the two mean values (confidence probability - p). Calculations were made on a personal computer using Microsoft Excel programs adapted for medical and biological research.

RESULTS AND DISCUSSION

The main clinical symptoms in children with rotavirus infection were: hyperthermia, vomiting and diarrhea. At an objective examination of children with RVI patients, reduced elasticity of the skin and turgor of soft tissues was revealed, which is a manifestation of exclusion due to the general dehydration of the organism. Children with RVI with deep palpation of the abdomen noted pain in the epigastrium and umbilical region, as well as rumbling along the intestinal tract. Moreover, clinical signs I and II had no significant differences ($p > 0,05$). In children with RVI with modified treatment, signs of general weakness disappeared by 1.17 days ($p < 0.001$) earlier than in children receiving standard therapy. For patients in this group, the duration of treatment was characterized by a reduction in the duration of swelling and / or abdominal pain by 0.72 days ($p < 0.05$) compared with standard treatment children. In patients with modified treatment, the raised body temperature was shorter by 0.52 days, compared with standard treatment ($p < 0.05$). In addition, patients in group II reduced the duration of diarrhea by 1.13 days ($p < 0.001$), and shortened vomiting by 0.6 days ($p < 0.001$) compared with children in group I. Along with this, there was no significant difference between the I and II groups regarding the duration of clinical symptoms such as pallor of the skin and appetite disturbance ($p > 0.05$).

In the period of the onset of the disease in patients with rotavirus infection (the main group) it was observed a significant reduction of IgA levels (0.58 ± 0.02) g / l compared to the similar indicator of children in the control group (0.82 ± 0.02) g / l ($p < 0.001$) (Table I). While the concentration of IgM was (1.01 ± 0.02) g / l and was significantly higher than the similar indicator of the control group (0.73 ± 0.02) g / l ($p < 0.001$), and the IgG level (8,42 ± 0.18) g / l did not differ significantly from the children in the control group (7.96 ± 0.21) g / l ($p > 0.05$). The secretory IgA in coprofiltrate in patients with CVI decreased to (23.15 ± 0.42) mg / l in relation to the data of virtually healthy children (31.18 ± 0.63) mg / l ($p < 0.001$).

The period of reconvalescence in children of group I after the traditional treatment was characterized by an increase in IgA to (0.71 ± 0.02) g / l ($p < 0.001$) and IgG (9.32 ± 0.19) g / l ($p < 0, 05$). While the concentration of IgM before discharge from the hospital decreased and it was (1,03 ± 0,03) g / l ($p > 0,05$). The level of secretory IgA in coprofiltrate in sick children increased and amounted to (27.10 ± 0.31) mg / l ($p < 0.001$).

Patients in the 2nd group, who received a probiotic drug in addition to traditional treatment, showed normalization of serum immunoglobulin A, M, G, and secretory immunoglobulin A in coprofiltrate.

The results of many studies indicate a positive effect of probiotic drugs on the course of acute and persistent diarrhea [13, 14]. In the study, researchers point to a decrease in the duration of diarrhea in children with acute intestinal infections, which was additionally designated *Bacillus clausii* [15]. Currently, the most well documented probiotic bacteria used in human therapy are lactic acid bacteria. In contrast, studies aimed at studying the mechanisms responsible for the probiotic positive effects of Bacillus are rare.

Table I. Dynamics of indicators of humoral immunity in children suffering from rotavirus infection, depending on the performed therapy, M ± m

Immunological index	Control group (n=28)	Main group		
		before treatment (n=65)	after treatment (n=65)	
			I group (n=34)	II group (n=31)
	1	2	3	4
Ig A, g / l	0,82 ± 0,02	0,58 ± 0,02 $p_{1-2} < 0,001$	0,71 ± 0,02 $p_{1-3} < 0,001$ $p_{2-3} < 0,001$	0,86 ± 0,03 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$
Ig G, g / l	7,96 ± 0,21	8,42 ± 0,18 $p_{1-2} > 0,05$	9,32 ± 0,19 $p_{1-3} < 0,001$ $p_{2-3} < 0,05$	9,11 ± 0,22 $p_{1-4} > 0,05$ $p_{2-4} > 0,05$ $p_{3-4} > 0,05$
Ig M, g / l	0,73 ± 0,02	1,01 ± 0,02 $p_{1-2} < 0,001$	1,03 ± 0,03 $p_{1-3} < 0,001$ $p_{2-3} > 0,05$	0,79 ± 0,03 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$
sIg A, mg / l	31,18 ± 0,63	23,15 ± 0,42 $p_{1-2} < 0,001$	27,10 ± 0,31 $p_{1-3} < 0,001$ $p_{2-3} < 0,001$	30,32 ± 0,39 $p_{1-4} > 0,05$ $p_{2-4} < 0,001$ $p_{3-4} < 0,001$

Notes: p_{1-2}-the reliability of the difference between the indicators of the primary group's children before treatment and the control group; p_{1-3} – the reliability of the difference between the indicators of children in group I after treatment and control group; p_{2-3} - the reliability of the difference between the indicators of the children of the main group before treatment and Group I after treatment; p_{1-4} - the reliability of the difference between the indicators of children of group II after treatment and the control group; p_{2-4} - the reliability of the difference between the indicators of the children of the main group before treatment and the second group after treatment; p_{3-4} - the reliability of the difference between the indices of children of the 1st and 2nd groups after treatment.

In the work of Urdaci, M. C., Bressollier, Ph., Pinchuk, I. (2004) evaluation of the immunomodulating properties of probiotic strains of B. clausii was performed in vitro on Swiss and C57 Bl / 6j mouse cells. The authors demonstrate that these strains in their vegetative forms are able to induce the activity of NOS II synthetase, IFN-γ production and the proliferation of CD4 + T cells [16].

The results of our study showed a decrease in the concentration of class A immunoglobulin and an increase in IgM in children with rotavirus infection, which may indicate the activation of the antibody formation in the acute period of the disease, against the background of an increased local response to antigenic stimulation in the intestine. Decreased IgA concentrations may be due to immaturity of the immune function of the intestine in young children and / or poor adhesion of the virus and neutralizing ability. At the same time, a slow "immunological start" or transient hypogammonoglobulinemia in young children may explain insufficient IgG and IgA levels during the infectious process. During the treatment of children with rotavirus diarrhea in the acute period of the probiotic preparation containing *Bacillus*, there was a rapid positive dynamics of the course of the inflammatory process: the immunological parameters reached the level of children in the control group.

So, the probiotic drug containing *Bacillus clausii* has a positive effect on the humoral immune system in children with rotavirus infection.

According to the results of our study, it was found that in children with rotavirus infection a decrease in the level of immunoglobulin of class A and an increase in IgM was observed. A low level of IgA during the infectious process may be due to immaturity of the immune function of the intestine in children or a slow "immunological start" in and / or poor adhesion of the virus and neutralizing ability. An increase in Ig M may indicate activation of the antibody formation in the acute period of the disease, against the backdrop of an increased local response to antigenic stimulation in the intestine. When included in the treatment of children with rotavirus diarrhea in the acute period of the probiotic preparation containing *Bacillus clausii*, there was a rapid positive dynamics of the course of the inflammatory process: reduction of clinical symptoms and normalization of immunological parameters.

Thus, the use in the complex treatment of rotavirus infection of a probiotic drug containing *Bacillus clausii*, contributed to improving the effectiveness of treatment.

CONCLUSIONS

1. The inclusion of *Bacillus clausii* in the treatment of children with rotavirus infection contributed the reduction in the duration of clinical symptoms.
2. In children with rotavirus infection in the acute period of the disease, there was a decrease in the concentration

of IgA and an increase in the level of IgM in serum and a decrease in sIgA in coprofiltrate.

3. During the period of reconvalescence in children with rotavirus infection after standard treatment, the humoral link of the immune system was characterized by improvement of the indicators, however, they did not reach the level of control group children.
4. In patients with rotavirus infection, which had been added to the traditional treatment with *Bacillus clausii*, the indices of the humoral immune system reached the level of control group children.

Prospects for further research: It will be perspective to further studying the effects of this probiotic drug on other parts of the immune system of children.

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