

Rotavirus Infection in Children as of Today (Literature Review)

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ABSTRACT

Urgency of the issue of rotavirus infection (RV) is stipulated by a special place in the structure of morbidity and mortality among young children. According to the data provided by WHO, 180 million diarrheal diseases with rotavirus etiology are registered every year. In Europe, 25 million children at the age of 5 years and younger are in need of medical care, and there are 2 million among them hospitalized each year. The specific prophylaxis is recommended in order to prevent these phenomena. Rotarix vaccine, which has cross protection against different strains (G1, G2, G3, G4 and G9), and RotaTed vaccine containing G serotypes (human serotypes G1, G2, G3, G4 and P1A and bovine serotypes G6, P7) are recommended. It has cross-protection against different strains.

Key words: children, rotavirus infection, prophylaxis.

Urgency of the issue of rotavirus infection (RV) is stipulated by a special place in the structure of morbidity and mortality among young children. According to the data provided by WHO, 180 million diarrheal diseases with rotavirus etiology are registered every year. In Europe 25 million children at the age of 5 years and younger are in need of medical care, and there are 2 million among them hospitalized each year. According to the data provided by Center for Disease Control and Prevention, in the United States 2.7 million cases are recorded among children of abovementioned age category, up to 70 thousand children are hospitalized and part of these cases has fatal outcome. On the basis of results of epidemic control of

rotavirus infection among children at the age of 5 years and younger, 46% of this pathogen of all intestinal infections are confirmed under laboratory conditions in Africa, 40% – in the countries of Middle East and South-East Asia, and 38% – in the countries of East Basin of Pacific Ocean [1].

The scientists who studied the incidence and mortality rates for the period 2000-2013 noted that the worldwide number of deaths caused by rotavirus in children at the age of 5 years and younger was 528000 in 2000 and in 2013 it was 215000. In 2013, 47100 deaths caused by rotavirus infection occurred in India, and 22% of all deaths are accounted for this pathogen. Four countries (India, Nigeria, Pakistan and Democratic Republic of the Congo) accounted for about half (49%) of all projected deaths caused by rotavirus infection in 2013 [2].

In accordance with the data published by PubMed, the prevalence of rotavirus infections among children in China is 33.1%; in particular, children at the age of 24 months and younger were more susceptible to RVA infection with the level of infection up to 87.4% [3].

The scientists who conducted the studies in order to assess the prevalence of aforementioned infection and examined the strain genotypes of rotavirus, which causes acute gastroenteritis in children at the age of 5 years and younger in Iran, detected rotavirus in 28.37% of total number of samples taken and recorded 72.91% of cases, which took place during the first 2 years of their life ($p = 0.038$). The highest infection prevalence was detected during summer period (52.5%) and the lowest prevalence was in winter period (7.50%) [4].

And on the contrary, in the countries with temperate climate the highest level of rotavirus gastroenteritis prevalence is observed during winter-spring period [5]. The frequency of rotavirus detection is 44% in January-February, and in other months this parameter is equal to 16.7% [1]. According to the data published by the regional office of WHO, in the territory of former Soviet Union in the past decade 24% of the acute rotavirus

enteritis among intestinal infections were recorded in Azerbaijan, 37% – in Georgia, 25% – in Kyrgyzstan, 28% – in Tajikistan, 30% – in Uzbekistan and 44% – in Ukraine [6]. In 2000-2010, the incidence rate in Ukraine ranged from 0.93 to 3.18 per 100 thousand people (disagreement, clinical immunology). According to the data provided by different authors, in recent years the share of rotavirus diarrhea ranges from 35% to 75% in different countries with a tendency to constant growth [7].

In the world, rotaviruses are accounted for more than 25% of the deaths associated with diarrhea and 6% of the deaths among children at the age of 5 years and younger. Particularly in developing countries, rotavirus infection causes more than 850000 deaths each year [8].

For a long time medical professionals believed that rotavirus infection had only intestinal manifestations. However, in 1978 the first publications on the impairment of central nervous system by rotavirus, which results in convulsions, development of intussusception, erythema, heart and liver damage, occurred. Thus, in the retrospective studies of the group of infants with convulsions hospitalized in the Primary Children's Medical Center, Salt Lake City, Utah, during the period from January 1, 2002, and December 31, 2006, the patients with rotavirus infection confirmed under laboratory conditions were detected. Afebrile convulsions at early stages were recorded in 68% of children [9]. The fact that rotavirus infection can cause neurological symptoms in young children was also established. However, the next question remains: why rotavirus infection has been missed as the cause of convulsions in infants for many years despite the significant research interest in neonatal rotavirus infection? [10]

Also, rotaviruses are the most common cause of nosocomial infections in young children. 9.6% to 69% of healthcare-associated intestinal infections are connected with this infection. The rotavirus is determined in 50-70% of infants. The level of virus carriage in children is 1.5-95%, including neonatal period – 71%.

The etiological characteristics of pathogen include the fact that this virus belongs to the Reoviridae family; it received the genus name in 1978 (“rota” means wheel); this virus has size of 65-75 nm. According to antigenic properties, the rotaviruses are divided into 9 serotypes, among which 1-4 and 8-9 serotypes are pathogenic for humans and 5-7 serotypes are found in animals. All human rotaviruses are divided taking into account the group-specific antigens, which are represented by proteins with inner capsid (A, B, C, D, E, F, G). However, 90% of rotaviruses, which are pathogenic for humans, refer to the Group A. On the basis of proteins with outer capsid, the rotaviruses are divided into G- (VP4) and P- (VP7) subtypes. G1-G4 are the most common rotaviruses worldwide. G1-type has been dominating for many years, but recently G2, G3 and G9-types started prevailing. P4 and P8 are the most common types among P-types. However, the combinations of both types G1P8, G2P4, G3P8, G4P8, which cause the development of diarrhea, are the most widespread. Due to such heterogeneity recurrent cases of this disease are recorded [1]. Also, there are results of the studies, which indicate that P6 strains of RV are the most common types in Africa [11].

The virus has three membranes: outer layer (protein coat), inner capsid and core. RNA of the virus is unique; it consists of two strands and has 11 segments, which encode 6 structural proteins (VP1-VP4, VP6, VP7) and 6 non-structural proteins (NSP1 – NSP6). Each protein is encoded by genomic segment, except for non-structural proteins 5 and 6 (NSP5, NSP6), which are encoded by the same segment. Two structural proteins - VP7 (glucoprotein or G-protein) and VP4 (P-protein split by protease) form the outer shell. The inner shell mostly consists of protein VP6, which is important for testing in order to determine antigens. NSP4 is the most probable virulence factor among the non-structural proteins. Presence of two protein capsids makes rotaviruses highly resistant to acidic stomach contents, gall, proteolytic enzymes and disinfectants [7].

Rotaviruses are quite resistant to freezing and ultrasound but they are susceptible to boiling, action of acids and alkalis. They live in faeces for the period up to 7 months; they can be kept in tap water at the temperature of 40°C for 2 months, on the vegetables at $t = 4^{\circ}\text{C}$ for 30 days.

The source of rotavirus infection is the sick person who discharges virus with saliva, urine and faeces. Discharge of causative agent lasts for 3-6 days till the occurrence of clinical symptoms in 20-30 days. The cases of chronic diarrhea up to 66-450 days are described in literature [1].

The infection has faecal-oral mechanism of transmission; it spreads through contact-household, food and water channels. Children at the age from 6 to 24 months are the most frequently affected. After the first infection, protection against the further infection is formed in 40% of children. The next cases of disease protect against the severe course. Recurrent cases are possible after 3 months.

For a long time pathogenesis of rotavirus gastroenteritis was considered in quite simplified manner, and the following aspects were marked out: the virus gets into gastrointestinal tract through mouth. The virus replication takes place in enterocytes, which results in their dystrophy and necrotic changes. At the same time, the inflammatory response with increased infiltration develops, and it results in the acute enteritis with villous atrophy and catarrhal colitis. Also, the lack of enzymes, which split disaccharides, is observed and it causes the increase of osmotic pressure, which draws water and prevents its absorption resulting in diarrheal syndrome [5].

But the knowledge of the fact how rotavirus penetrates into human cells turned out to be very significant factor. Despite the progress made over the last decade in comprehension of the mechanisms, which explain the pathogenesis of rotavirus infection, there are many unsolved issues associated with the processes of rotavirus entry and internalization. The major

question is whether rotaviruses have alternative channels of entry, in particular, whether they can inhibit any of suggested receptors; also, it should be noted that the specialists have not succeeded in complete prevention of the virus at this stage. In order to enter into the target cell, rotaviruses use three types of cell surface molecules: 1st type includes the molecules, which bond molecules represented by SA and certain integrins; 2nd type represents chaperoning molecules, including Hsc70 and other heat shock proteins; and 3rd type represents reduction-oxidation molecules including PDI, ERp57 and other molecules related to thioredoxin. Currently, the receptors for rotavirus, which fall into these main categories of molecules and support entry mechanisms, have been established. But other molecules, which have not been revealed yet, can also fulfill the same functions in other cell types and for other strains of rotavirus. Scientists have discovered the universal mechanism for the entry of rotavirus infection but the receptor molecules, which implement the entry mechanism, may differ in part or in whole depending on the type, cell line and rotavirus strain.

Receptor use and rotavirus tropism are determined by certain number and location of receptors on the surface of host cell. Rotavirus structural proteins involved at the early stages of virus life cycle are the substrates of cell surface molecules, which contain oxidoreductase, thiol isomerase and Chaperone mechanisms responsible for the conformational changes of virus proteins, which interact and are necessary for internalization.

Further studies should emphasize and determine the reasons why many receptors are used by rotaviruses. The fact that rotaviruses cause oxidative stress makes it possible to develop new therapeutic strategies for the inhibition of rotavirus infection and reveals the new method for treatment of life-threatening rotavirus diarrhea and supplement of existing vaccines. However, the main shortcoming in the comprehension of rotavirus infection strategy is the fact that rotaviruses resist the anti-inflammatory warning for replication but anti-inflammatory treatment inhibits the virus infection. This gap is a serious problem because

more detailed characteristics of the molecular mechanisms, which form the basis of rotavirus-induced inflammatory warning, are needed. Another unsolved issue consists in the comprehension of rotavirus-induced oxidative stress and fact how antioxidant inhibits the virus infection during the treatment process [12].

Scientists express an interesting scientifically-based opinion on rotavirus entry into the host cell, which takes place through successive interactions between virion proteins and different host cell surface molecules. The mechanisms of entry are associated with cell molecules, which have chaperoning and oxidative processes. The receptor use and rotavirus tropism are determined by the type, cell line and rotavirus strain. As of today, the rotaviruses have evolved and they can resist the innate immune response, and at the same time they are capable to induce the endoplasmic reticulum (ER), oxidative stress and inflammatory signal transmission. The connection between ER stress, inflammation and oxidative stress is implemented with the release of calcium from ER, which increases the generation of mitochondrial reactive oxygen species (ROS) and results in toxic accumulation of reactive oxygen species in ER and mitochondria. Gradually, the stress potentially stimulates inflammatory response through the protein reaction paths. However, there is no detailed characteristic of molecule mechanisms, which form the basis of these induced stress conditions of rotavirus action. Signal events initiated by the recognition of host-virus associated molecule models enable the scientists to develop new therapeutic strategies aimed at the interference with rotavirus infection and reveal new methods for the development and supplement of vaccines [12].

Early studies of rotavirus infection revealed the reduction of SOD and glutathione peroxidase in the intestine of tested young mice [13]. More recent study showed that rotavirus infection is able to induce the increase of inducible nitric oxide synthase (iNOS) of mRNA and expression of iNOS when exposed to NSP4 [14]. NSP4-induced release of NO from

metabolites was detected in the culture of human intestinal epithelial cells [15]. Scientists recorded the increase of values of oxidative stress indices, including malondialdehyde (MDA) and NO concentration in blood serum, which were also associated with the pathological condition [16].

Connection of secretory diarrhea with NSP4 has significant importance in the study of rotavirus infection pathogenesis; NSP4 is a non-structural protein, which acts as bacterial enterotoxin disrupting the intracellular metabolism of calcium, potassium, sodium, chlorine and water and affecting the nerve terminals. It results in the accumulation of calcium inside the cells and causes the excretion of potassium, sodium, chlorine and water into the intestinal lumen. Disturbance of ion exchange and accumulation of proteins, which are foreign for the host organism and necessary for virus particle formation, cause the desquamation of enterocytes [1].

The clinical pattern of rotavirus infection is represented by various forms, gastroenteritis and gastroenterocolitis, in general. The incubation period is 1-5 days. Some experts described the symptomatology as DFV-syndrome (diarrhea, fever, vomiting) [1].

Basically, the following sequence of syndromes is observed: first 3 days – catarrhal syndrome with hyperthermia on the 3rd day up to 38-39°, respiratory syndrome on the 3rd-4th day, then dyspeptic and intoxication syndromes. Defecation is foamy, watery with strong odor up to 5-20 times a day; there are imperative feelings of defecation.

The severity of the child state is also stipulated by dehydration. The acetonemic syndrome (Cyclic Vomiting Syndrome – CVS syndrome) is observed in 81.1% of children who are older than 1 year; the frequency of vomiting increases by 15 times [1, 17].

The scientists explain such phenomena by the disorders in Krebs cycle – the universal method of energy conservation. Lipolysis stimulation is the metabolic basis of this syndrome. Fatty acids are transformed into acetyl-CoA in the liver. Under normal conditions, the basic

method of acetyl-CoA metabolism consists in the reaction with oxaloacetate with the further generation of energy. Part of acetyl-CoA is used for resynthesis of fatty acids and cholesterol. Only small portion is used for the formation of ketone bodies. In case of intense lipolysis, the excessive amount of acetyl-CoA is produced. Also, the activity of enzymes, which activate resynthesis of cholesterol and bile acids, decreases. As a result, there is basic method of acetyl-CoA utilization – formation of ketone bodies. Their level exceeds the functional capabilities of liver to utilize them, and it results in ketonemia, metabolic acidosis, ketoacidosis at the first stage; at the expense of condensation of 2 molecules of acetyl-CoA, the acetyl-CoA, which is metabolized into acetoacetic acid passing to ketone bodies – acetone and β hydroxy-butyric acid, is formed. First, the compensation of metabolic disorders takes place at the expense of hyperventilation, which causes hypocapnia and vasospasm, including cerebral vessels. Also, for the utilization of ketone bodies the additional quantity of oxygen is needed; it will cause the difference between supply and consumption. Penetrating into CNS, ketone bodies have adverse effect on the brain, they damage the lipid layer of cell membrane and irritate the vomiting center. Also, when there is vomiting, gastrointestinal tract is irritated and abdominal syndrome is observed. Ketone bodies are discharged through kidneys and respiratory organs, and it results in ketonuria and occurrence of acetone odor in exhaled air. Children with CVS syndrome are at risk group with regard to the development of diabetes during adolescence [17]. As is well-known, Taylor formulated the virus theory of development of diabetes of the 1st type, the incidence rate of which has significantly increased in the world as of today [18]. Thus, in the authors' opinion the study of the prevalence of development of diabetes of the 1st type in children at the age of 5 years and older with genetic susceptibility and recurrent rotavirus gastroenteritis with accompanying acetonemic syndrome can be one of the urgent issues for the research by scientists, which has been analyzed to a small degree so far. The scientists who compared the data of ultrasound examination of

abdominal cavity organs in children with rotavirus infection have detected echocardiographic changes of pancreas in 66.6% and recorded the increase in echogenicity and granularity of parenchyma against the background of organ enlargement [7].

Authors who studied the immunological changes in the body of sick person noted that at the early stage of disease the protection takes place at the expense of secretory IgA (sIgA). In several days, IgM are included, and during rotavirus discharge from organism the antibodies to IgG occur providing the easier disease course in case of reinfection. The inhibition of cellular component, in particular T-helpers, and destruction of phagocytosis are observed. During the acute phase, the increase of serum interferon is noted; on the 7th-8th day their decrease is noted, however, the function of interferon production of leukocytes is still reduced.

Scientists established that interleukin 8 influences on the tissue immunity; the higher its level is, the more rotavirus antigens are in blood and at the same time IL-10 decreases [1].

Scientists who studied the levels of microelements noted the decrease of zinc, phosphor and copper and increase of iodine and iron in blood serum samples in 44.4% of cases [7].

The most common method of diagnostics consists in the detection of rotavirus antigen in stool samples using immune-enzyme assay. Electronic microscopy, reverse polymerase reaction, nuclein-acid hybridization, sequencing and virus culture examination, serological diagnostics can be used for scientific studies. Recently, the detection of rotavirus is performed using “cito test rota”.

The differential diagnosis of rotavirus gastroenteritis is carried out with various intestinal infections using bacteriological and virological studies of vomit mass and excrements. The prior clinical diagnosis can be made on the basis of symptomatology. Cholera starts with diarrhea and vomiting occurs later; it is not accompanied by catarrh of the upper respiratory tract and abdominal pain. The following symptoms are typical for

salmonellosis: abundant and foamy mud-colored excrements, prolonged fever, enlargement of liver and spleen, leukocytosis. In case of dysentery, the syndrome of hemorrhagic colitis is the basic symptom. Adenovirus infection, at which rhinopharyngitis can also be combined with enteritis syndrome, is characterized by conjunctivitis, polyadenitis, enlargement of liver and spleen [1]. With rotavirus infection, such symptoms include secretory diarrhea and enteritis phenomena. There are several degrees of dehydration: mild degree – liquid loss up to 5% of body weight; moderate degree – liquid loss of 5% to 10% of body weight; severe degree – liquid loss of more than 10% of body weight. According to the content of electrolytes in the blood of patients with dehydration, in particular sodium, which is part of the extracellular fluid of organism and its osmolarity, three types of dehydration are determined: water-deficient type, salt-deficient type and isotonic type. Monitoring of metabolic disorders is carried out according to the changes of parameters of acid-base balance, electrolytes and gas composition of venous blood.

Patients with moderate and severe disease course are hospitalized. The diet is prescribed during the acute period. Timely and adequate compensation for water and electrolyte loss is the basis of treatment. As of today, rehydration is divided into oral and parenteral forms. In order to perform rehydration it is necessary to determine the following parameters: daily demand for liquid, type and degree of dehydration, current pathological losses, total deficit of liquid; also, it is required to determine the method of rehydration [19].

Oral (peroral) rehydration should be the first therapeutic measure, which is implemented at home with the occurrence of the first symptoms of disease. Rehydration is performed till the restoration of the volume of lost liquids and lasts for 4-6 hours. Rehydration is ineffective when dehydration increases, vomiting, profuse diarrhea, toxicosis symptoms continue; then, the infusion therapy is used.

It is required to calculate the rate of administration and daily volume of liquid, which is essential for child, using J. Dennis method: 1st degree of dehydration: children at the age of 1 year and younger – 140-170 ml/kg; children at the age of 1-5 years – 100-125 ml/kg; older children – 75-100 ml/kg. 2nd degree of dehydration: children at the age of 1 year and younger – 160-180 ml/kg; children at the age of 1-5 years – 130-170 ml/kg; older children – 110 ml/kg. 3rd degree of dehydration: children at the age of 1 year and younger – 200-220 ml/kg; children at the age of 1-5 years – 170-180 ml/kg; older children – 120-150 ml/kg. The most optimal solutions of crystalloids for parenteral rehydration in infants include 5% solution of glucose and 0.9% solution of sodium chloride and special solutions for parenteral rehydration. In case of isotonic dehydration, the volume ratio of 5% glucose solution and 0.9% NaCl solution is equal to 1:1. In case of hypertensive dehydration, the volume ratio of 5% glucose solution and 0.9% NaCl solution is equal to 3:1. In case of hypotonic dehydration, the volume ratio of 5% glucose solution and 0.9% NaCl solution is equal to 1:2. Potassium is the compulsory component of infusion therapy – Asparaginat K-Mg at the dose of 1 ml/kg per day. Contraindications for intravenous administration of potassium medicine include anuria or pronounced oliguria (less than 20 ml of urine per kg of body weight for 1 hour). 1-2 ml/kg/day of 10% solution of calcium gluconate are added in case of the 3rd degree of dehydration, pronounced microcirculation disorders, toxic, acidotic breathing, impairment of consciousness; 4% solution of sodium bicarbonate at the dose of 4 ml/kg/day is used. Properly performed infusion therapy is accompanied by elimination of dehydration symptoms in the first 24 hours. Then, it is required to calculate the volume of rehydration therapy for the following days: children at the age of 6 months and younger – 120-100 ml/kg; children at the age of 6 months-2 years – 100-80 ml/kg; children at the age of 2 years and older – 80-40 ml/kg.

The use of enterosorbents significantly reduces diarrhea duration. Enterosorption duration is 5-7 days.

The indications for antibacterial therapy in case of secretory diarrhea include children with immunodeficiency state and HIV-positive children who are on immunosuppressive therapy or having hemolytic anemia. Currently, the course of antibacterial therapy is recommended to be stepwise (3 days – parenteral method of administration, 2-5 days – enteral administration of medicine of macrolides or cephalosporins. Immunoglobulin of enteral origin is used in the treatment of rotavirus diarrhea: anti-colitis lactoglobulin, anti-rotavirus immunoglobulin, complex immunoglobulin medication for oral administration, triglobulin [19, 20].

Performed analysis of the data of systematic reviews of PubMed source demonstrates high interest of researchers in the study the clinical effects of the substances isolated from sea-buckthorn leaves (*Hippophae Rhamnoides L.*); there are about 20 studies, which confirm the great therapeutic potential of immunomodulatory, anti-inflammatory, protective, antioxidant, hepatoprotective and antimicrobial action [21].

Adjuvant therapy is applied for the correction of dysbiotic disorders of intestinal microbiocenosis using prebiotics, probiotics, symbiotics; they are prescribed for the period of 1-2 months taking into account the coprogram data, examination results of faeces for dysbiosis. The most effective probiotics in case of intestinal infections include the following medicinal products [20].

Children who have recovered from severe form of rotavirus infection are subject to dispensary observation for six months. The patients are isolated for the period of 10-15 days. Current and final disinfection of premises, chamber treatment of clothes and bed linen are performed. The specific prophylaxis procedure is developed [22]. There are two live attenuated rotavirus vaccines. Rotarix is monovalent, peroral, freeze-dried vaccine restored by

the buffer CaCO₃; it contains the human strain G1P8 and has cross protection against different strains (G1, G2, G3, G4 and G9). It is administered by two doses with OPV1, OPV2. RotaTed is pentavalent liquid vaccine containing G serotypes – human G1, G2, G3, G4 and P1A serotypes and bovine serotypes – G6, P7. It has cross protection against different strains; it is administered with OPV1, OPV2, OPV3 in three doses [6, 23].

Rotavirus vaccine is recommended for routine use in all countries of the world. In order to facilitate the process of decision making with regard to the use of rotavirus vaccine by the countries, researchers evaluated the mortality of children at the age of 5 years and younger caused by rotavirus during the period 2000-2013, and they collected and analyzed data in 1998. The studies were performed using immune-enzyme assay. Scientists also included the data obtained from the countries, which participated in the World Health Organization (WHO), coordinated rotavirus surveillance network for the period 2008-2013 where these criteria were received. In order to predict the fate of diarrhea due to rotavirus, they built multiple linear regression models, studied the annual evaluations of certain countries. The result of this research contains the following information: rotavirus vaccine was administered in more than 60 countries worldwide by the end of 2013. Countries using the anti-rotavirus vaccine during the reporting period had low mortality rate; however, the impact of rotavirus vaccine in global evaluations of rotavirus mortality has limited character. Scientists continue to monitor rotavirus mortality via observation, and this fact assists in the spread of vaccination against this pathogen among children in many countries of the world [2].

Conclusion. Thus, due to the deterioration of the coverage of vaccination in Ukraine in 2013-2016 and absence of mandatory vaccination against rotavirus infection at the state level, we have the task on reduction of the cases of rotavirus infection among children by improving the epidemic control, clinical detection, instant testing, proper treatment and promotion of vaccination; it is the key to health of the nation as European country.

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