Diarrhea with Rotavirus in Children

CRISTINA SINGER, POLIXENIA STANCU, SIMONA COŞOVEANU, LOREDANA OSIAC, COCA GRIGORIE, ALINA BOTU

Pediatrics Department, County Emergency Hospital Craiova, University of Medicine and Pharmacy, Craiova

ABSTRACT The rotavirus is the most frequent etiologic agent of the acute diarrheic disease in infants and young children worldwide. It is globally estimated that rotaviruses are annually responsible for more than 111 million cases of infantile gastroenteritis and approximately 600,000 deaths. As a result of the high morbidity and mortality, the diarrhea with rotavirus represents a major health problem. The research in the field of the antirotaviral vaccination revealed new possibilities of reducing the frequency of the diarrhea caused by this virus. The present paper contains the disease epidemiology, morphology, pathogeny, transmission, clinical aspects, diagnosis, treatment and prevention.

KEY WORDS rotavirus, diarrhea, children

Introduction

The rotavirus is the most frequent etiologic agent of the acute diarrheic disease in infants and young children worldwide. It is globally estimated that rotaviruses are annually responsible for more than 111 million cases of infantile gastroenteritis and approximately 600,000 deaths. Lethality is highest in the developing countries (23).

In the first five years of life, every child can be virtually infected with this pathogen agent, no matter the race or the socio-economic status (24).

The costs estimated for hospitalizing the severe forms of rotavirus diarrhea are over 1 billion dollars yearly.

Epidemiology

The rotavirus is ubiquitous and up to the age of 3-5 years 95% of the children around the world are infected (22).

From the first discovery of the rotavirus in 1973, one has established that this infectious agent represents the most frequent cause for severe gastroenteritis, with SDA in infants and small children, both in the developed countries and in the developing ones. Worldwide, it is estimated that the rotavirus causes annually 111 million episodes of gastroenteritis in children who need only home care, 25 million cases needing a medical examination, 2 million with hospitalization and a death average of about 600,000 cases. This means that up to 5 years of age, almost all children will have presented an episode of gastroenteritis with rotavirus, 1 out of 5 children needing medical examination, 1 out of 65 hospitalization and 1 out of 293 dies (23, 24).

In the temperate climate, the rotavirus diarrhea mainly occurs during the cold season, while in the tropical regions and in the developing countries, the seasonal character is less obvious (8).

Rotavirus morphology

The rotavirus genus belongs to the Reoviridae family. The icosahedral, non-enveloped viral particle has a diameter of 70 nm and it is made up of 3 concentric protein layers (capsids) which surround the genome. The 3 protein layers have capsid subunits of the capsid (capsomeres) with a radiant disposition from the inner to the outer capsid, providing the viral particle a distinct morphology, wheel-like appearance (from the Latin “rota”= wheel) by electronic microscopy (16) (figure 1).

Figure 1. Schematic representation of the rotavirus virion

The viral genome is structured in 11 segments of double-stranded RNA. Each segment encodes structural and non-structural viral proteins (22).

The outer layer of the viral particle is made up of 2 surface viral proteins (VP7 and VP4) which have antigenic properties.
The middle capsid is made up of VP6 which forms more than 50% of the virion. The core is composed of VP1, VP2 and VP3 proteins. The VP3 and VP6 proteins are necessary for the RNA transcription and for a correct viral structure (19).

In addition to the 6 structural proteins, there were identified 5 nonstructural proteins (NSP 1-5). Regarding the NSP function, there is little information, but it is considered that it may facilitate the viral replication (11, 19).

**Classification**

The rotaviruses have 3 important antigenic characteristics based on group, subgroup and serotype, which are determined by the proteins of the viral capsid (5) (figure 2).

![Figure 2. Classification of rotaviruses, modification](image)

Group specificity is determined by the VP6 protein of the middle capsid. On the basis of the antigenic properties of the VP6 protein, there were described 7 serotypes (A → G) (5).

Only the A → C serotypes infect people. The A serotypes produce, most frequently, gastroenteritis in infants and young children, both in the developed and developing countries. The B and C serotypes were occasionally associated with human illness (22).

Within the A serotype, depending on the proteins of the outer capsid, there were described P serotypes (depending on the VP4 protein) and G serotypes (depending on the VP7 protein) (22).

So far, there were identified 20 P serotypes and 14 G serotypes which, for man, are pathogens: P 4, P 6, P 8, P 9 and G 1- G 4. Both proteins, VP4 and VP7, stimulate the synthesis of neutralizing antibodies and can be involved in protective immunity; they also represent important targets for the vaccine production (5).

A large variety of rotaviruses can result from different combinations of G and P serotypes which infect people. Only 4 strains are more spread: G 1 P[8], G 2 P[4], G 3 P[8], G 4 P[8]. Most of the illnesses are attributed to the G 1 P[8] type (the genotype appears in square brackets) (9).

Important studies have shown that these 4 strains account for more than 88% of all rotavirus infections (27).

**Pathogeny**

The rotavirus adheres to the intestinal epithelium, the main proliferation area of the rotavirus being represented by the mature villus enterocytes located in the upper region of the small bowel. In 1-2 days, following the viral replication, the infection spreads from the proximal area of the small bowel to the ileum. The mucosal lesions occur as a result of the destruction of the villi, located along the gut (22).

The main mechanism for producing the rotavirus diarrhea is considered to be the decrease of the sodium and water absorption, as a consequence of intestinal lesions, and the replacement of the epithelial cells, with an absorption role, by secretory cells from the villous crypts (secretory diarrhea) (18). In the second phase, because of cell destruction, the level of the disaccharides will decrease and this will lead to carbohydrate malabsorption and osmotic diarrhea. The villi damage is reversible and the diarrhea continues until the villi regenerate (14).

Other mechanisms, too, can be involved (in the absence of mucosal lesions) in producing diarrhea. There is evidence that a nonstructural viral protein NSP4 (encoded by gene 10) can act as a viral enterotoxin (1, 20). One also believes that the rotavirus determines a fluid and electrolyte secretion, by activating the enteric nervous system which is located in the intestinal wall.

**Transmission**

The rotaviruses are highly contagious and the main transmission mode is the fecal-oral route (22). Since the virus is stable in the environment, the transmission can occur through person-to-person spread, ingestion of contaminated water or food, through contact with contaminated surfaces, such as toys or food preparation counters (7).

The rotavirus is resistant to common disinfectant products but it is inactivated by 95% ethylc alcohol (8).

The highly infectious nature of rotavirus and its stability in the environment represent a problem for healthcare facilities, the nosocomial infection being reported all over the world.

It is important to know that the asymptomatic excretion of the rotavirus occurs in half of the infected children before the onset of the clinical symptoms and persists in one third of the children...
in the week that follows the end of the symptoms (25).

Other routes of transmission, more rare, are the respiratory and the animal-to-man transmissions (22).

Morbidity is universal, the infection being frequent both in the developed and developing countries.

**Clinical picture**

Most studies indicate an incidence peak in the 6-24 months age group, although the disease, in the developing countries, is also frequent in infants younger than 6 months of age.

The first infection with rotavirus is usually severe and it confers a protecting effect against future rotavirus infections; if they continue to appear, they are less severe or asymptomatic (32).

Incubation is short (24-48 hours). The onset is sudden. The vomiting occurs at the disease onset and it is followed by diarrheic, watery stools (5-10/day). Fever and abdominal pains are frequent. Diarrhea and vomiting can produce medium or severe dehydration. They can last up to 9 days, while diarrhea usually lasts 21 days. In children with normal immune system and adequate nutrition, the infection is self-limited (13).

Other clinical features, such as anorexia and respiratory symptoms, as well as an increase of the liver enzymes, were associated with the rotavirus infection (4).

**Laboratory diagnosis**

Since the early 1980s, by means of rapid diagnosis techniques such as ELISA or EIA, the viral antigen (capsid protein) has been detected in stool specimens (17).

For research purposes, the virus can be identified by electronic microscopy (the characteristic wheel-like appearance), considered the standard diagnosis method, and by RT-PCR which highlights the G and P antigens (22).

**Treatment**

**Standard Treatment**

In the case of hydro-electrolytic and acid-basic disorders which are secondary to diarrhea and vomiting, the oral rehydration is recommended for the mild and medium forms of disease; in severe forms of dehydration, parenteral and then oral rehydration is recommended. The rehydration therapy treats the disease symptoms and not the cause and does not reduce the spread of the virus to other individuals (29).

As with all viral infections, antibiotics are not indicated, and at present there are no efficient antiviral agents against rotaviruses.

**Preventive treatment**

Passive immunity from the placentally transferred maternal antibodies and breast-feeding plays an important role in the protection against the occurrence of the rotaviral disease in young infants. That is why natural feeding is recommended; artificial feeding is associated with an increased risk of infection, as it was proved in a study carried out in England (15, 28).

Rigorous infection control practices in the neonate and pediatrics departments can help preventing the nosocomial infection with rotavirus.

Efforts to reduce the number of people getting sick and the number of deaths because of diarrhea aim at improving the water quality and the sanitation and at introducing the treatment programs based on oral rehydration. Although these efforts decreased the rate of mortality associated to infections with bacteria or parasites, they were insufficient in order to diminish the mortality and morbidity associated with rotavirus infection. Similar incidence of gastroenteritis with rotavirus in both developed and developing countries suggests that the problem cannot be controlled by these measures (10).

Because of the huge global economic pressure attributed to rotavirus infection, the development of vaccines against rotavirus represents the first-line prevention strategy. WHO has permanently supported the production of the vaccine against rotavirus ever since the beginning of the 1980s, recommending the introduction of a routine vaccination in children.

**Vaccination**

Clinical studies and the production of the vaccine against rotavirus began in the late 1970s, approximately 5 years after the virus discovery. The research mainly focused on the production of live-attenuated vaccines, with oral administration, since the immunity located at the level of the intestinal mucosa plays a major role in reducing the incidence and severity of the infection (11). Heterotypic protection was considered an important requirement (3).

The first model which was completely investigated was the monovalent bovine RIT 4237 vaccine which induced 88% heterotypical protection against severe diarrhea with rotavirus. Its production was halted in 1980 because its protecting efficiency was not fully confirmed (30).
After 15 years, in 1998, US Food and Drug Administration (FDA) licensed the first vaccine for rotavirus - RotaShield (Wyeth-Lederle), a tetravalent vaccine, recombined with human virus and rhesus, a live vaccine for oral administration (10).

In July 1999, less than 1 year since its launch, US-CDC recommended the suspension of RotaShield administration, the fact being related to the occurrence of rare cases of fatal bowel obstruction (12).

At present, there are two types of vaccine with an increased efficiency and demonstrated safety.

The ideal vaccine should protect against the moderate and severe forms of disease, to prevent deaths, hospitalization, and to reduce morbidity and the associated socio-economic costs, to decrease severity and the disease period of time for new cases, without producing any other disease. The perfect vaccine should be sufficiently immunogenic, in order to stimulate the production of neutralizing antibodies for the serotypes which cause most frequently the disease (8).

RotaTeq (Merck&Co) is a recombined, pentavalent, human-bovine vaccine, with a live virus and an oral administration. It contains 5 human–bovine recombined strains. Each strain contains gens of the bovine (WC3 strain) and human virus which encodes either the VP4 (P[8]) protein, or the VP7 (G1, G2, G3 and G4) protein. Both surface proteins (VP4 and VP7) stimulate the production of specific neutralizing antibodies. Rota Teq is administered in 3 oral doses in the first 6 months of life, at a time interval of at least 4 weeks between the doses; the first dose is administered in the 6 and 12 weeks of life interval (8).

Rotarix (GlaxoSmithKline) is a vaccine with a human monovalent, live-attenuated virus. It was approved in more than 63 countries and will be available in many others.

It was developed by using cloning and passaging in cell cultures from a precursor-attenuated strain 89-12, which was initially obtained from a child infected with rotavirus in Cincinnati. This strain 89-12 has the G,P,A serotype (genotype P[8]) (2). Although Rotarix contains only 1 G,P[A] type, it shares protecting epitopes, including those involved in neutralizing the virus, with numerous other types of human rotavirus belonging to other G types. This is due, first of all, to the presence of 11 human genes and the common epitopes of the VP4 protein which was identified as the neutralizing immune-dominant protein which occurs after the Rotarix inoculation (31).

2 oral doses are administered, in the first 6 months of life. The first dose can be administered from as early as 6 weeks of age, while the second after a minimum interval of 4 weeks. The vaccination must be completed by the age of 24 weeks (26).

Two retrospective trials, which summed up over 60,000 infants, demonstrated the efficiency of the two new vaccines (RotaTeq and Rotarix) against rotavirus diarrhea (8).

References


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