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ROTAVIRUS AND GASTROENTERITIS: CLINICAL AND EPIDEMIOLOGICAL TRAITS

ROTAVIRUS Y GASTROENTERITIS: RASGOS CLÍNICOS Y EPIDEMIOLÓGICOS

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ABSTRACT

There is a strong association between rotavirus and gastroenteritis. The gastroenteritis by rotavirus is one of the most important causes of child internation at hospital. The rotavirus belongs to the *Reoviridae* family, genus *Rotavirus* and it have been classified into seven groups (A to G), where the A group is the major cause of diarrhea in children, and the B group in adults. The symptoms of the rotavirus gastroenteritis are high fever, vomiting, and severe diarrhea, leading to dehydration. Subclinical and asymptomatic rotavirus infections are very common among adults. The detection of rotavirus is done by various methods. The treatment is the use of Oral Rehydration Salts, the control is made through epidemiological vigilance and the immunization is done by the use of vaccines (as RRV-TV, in the US market, and 89-12, still being tested). Was realized this bibliographic research using the international databanks SCIELO, BIREME, PUBMED and HIGHWIRE. The diarrhea caused by this virus is the most common severe infection in children younger than 5 years and it leads to approximately 440.000 deaths per year. By this way, efforts to discovery of vaccines more effective should be stimulated and the health workers must be prepared to detect these viruses to alert the epidemiological vigilance.

Keyword: Rotavirus; Gastroenteritis; Diarrhea; Children diarrhea; Viruses.

RESUMEN

Existe una fuerte asociación entre los rotavirus y la gastroenteritis. La gastroenteritis originada por rotavirus es una de las más importantes causas de hospitalización en niños. Los rotavirus pertenecen a la familia *Reoviridae*, al género *Rotavirus,* y ha sido clasificado en siete grupos (A-G), donde el grupo A es el mayor causante de diarrea en niños, y el grupo B en adultos. Los síntomas de gastroenteritis por rotavirus son fiebre alta, vómitos y diarrea severa, que conduce a la deshidratación. Las infecciones por rotavirus en adultos muy comúnmente son subclínicas y asintomáticas. La detección de rotavirus se realiza por varios métodos. El tratamiento utilizado es la Rehidratación Salina Oral, el control se realiza por vigilancia epidemiológica y la inmunización se realiza por el uso de vacunas (como RRV-TV, en el mercado norteamericano, y 89-12, aún en estudio). La investigación bibliográfica fue realizada utilizando los bancos de datos internacionales SCIELO, BIREME, PUBMED y HIGHWIRE. La severa diarrea causada por este virus es la infección más común en niños menores de 5 años y conduce aproximadamente a 440.000 muertes por año. Por este motivo, esfuerzos por descubrir vacunas más efectivas deben ser estimuladas y los trabajadores sanitarios tienen que estar preparados para detectar estos virus y alertar a las instituciones encargadas de la vigilancia epidemiológica.

Palabras clave: rotavirus; gastroenteritis; diarrea; diarrea infantil; virus.

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INTRODUÇÃO

The infant gastroenteritis is one of the greatest public health problems, it's also the cause of new borns and lactents`s high morbidity and mortality in countries in development (COSTA; CANDEIAS; CAPELETTI, 1990; SÁNCHES-FAUQUIER et al.,2004). The large number of children visiting a pediatrician or hospitalized with gastroenteritis is an indication of the continuing importance of this disease. Among the many viruses causing diarrhea, rotavirus is a common childhood infection (YOKOO; ARISAWA; NAKAGOMI, 2004; LINHARES, 2000; GRIFFIN et al., 2002) and it's the major cause of severe illness in infants and children throughout the world (COSTA; CANDEIAS; CAPELETTI, 1990; SANEKATA et al., 2003). Diarrhea in adults has also great rotavirus participation (COSTA; CANDEIAS; CAPELETTI, 1990). The rotaviruses are important acute gastroenteritis etiologic agents in animals of several species (COSTA; CANDEIAS; CAPELETTI, 1990; SAN MARTÍN et al., 2004).

Studies from temperate climates show a striking seasonal pattern of rotavirus infection, with most cases occurring during the colder months of the year. Based on studies of hospitalized patients, it has been shown that the highest frequency is usually observed in children younger than 5 years (FRÜHWIRTH et al., 2001).

In countries in development, especially, there are estimative that rotavirus associated gastroenteritis cause approximately 440.000 deaths each year (PARASHAR et al., 2003), numbers that represent 20 to 25% of the total deaths for diarreacal disease, as 6% of the global mortality among children less than five years old. In impacting numbers, each day dies 2.000 children with diarrhea caused by these pathogens (LINHARES,2000) 4. Each year, rotavirus causes an estimated 111 million episodes of diarrhea requiring only home care, 25 million clinic visits, and 2 million hospitalizations (PARASHAR et al., 2003). Within several rotaviruses groups, group A rotaviruses are the single most important cause of severe acute diarrhea in young children throughout the world (SÁNCHES-FAUQUIER et al., 2004; BISHOP et al., 2001).

Infection is localized in the intestine, and only rare reports suggest any morbidity resulting from extra intestinal involvement (LYNCH et al., 2001). The main clinical findings are fever, vomiting and deshidatation. The use of the Oral Rehydration Salts is an efficient method to treat the acute diarrhea (LINHARES,2000). Efforts are ongoing to develop rotavirus vaccines, and several candidates are undergoing clinical testing (PARASHAR et al.,2003), which would be the best way to fight this virus.

The detection of rotavirus is made by various methods, including EIA, immune electron microscopy, electron microscopy, RT-PCR (LYNCH et al., 2001) and ELISA (LINHARES, 2000; FRÜHWIRTH et al., 2001).

The objective of this study was evidencing the rotaviruses and gastroenteritis association, analyzing important aspects of this relationship, such as epidemiology, clinical and laboratorial diagnosis, prevention and treatment. To this objective, was used the bibliographical records of international databanks SCIELO, HIGHWIRE, BIREME and PUBMED.

ROTAVIRUSES

The rotavirus belongs to the *Reoviridae* family, genus Rotavirus (SAN MARTÍN et al., 2004; MASCARENHAS et al., 2002; BRUNET et al., 2000). The complete viral particle is constituted by a triple-layered shell protein and the genome that consists of 11 segments of double-stranded RNA (dsRNA) each one coding a protein (COSTA; CANDEIAS; CAPELETTI, 1990; SÁNCHES-FAUQUIER et al., 2004; MASCARENHAS et al., 2002). These segments can be separated by polyacrylamide gel, according to their molecular weight, varying from 2,04 x 106 to 0,23 x 106 daltons (COSTA; CANDEIAS; CAPELETTI, 1990; FRÜHWIRTH et al., 2001). The outermost layer of the virion is formed by two proteins, VP4 and VP7 (SÁNCHES-FAUQUIER et al., 2004; SAN MARTÍN et al., 2004; BISHOP et al., 2001), encoded by RNA segment 7, 8, or 9 (depending on the strain) and segment 4, respectively (SÁNCHES-FAUQUIER et al., 2004), which are responsible for early interactions of the virus with its host cell (i.e., the attachment of the viral particle to specific cellular receptors and the penetration of the virion into the cell's cytoplasm) (SAN MARTÍN et al., 2004). These viruses have been classified into seven groups (A to G) by means of VP6 serology, genomic RNA, eletrophoretic patterns and group-specific PCR (SANEKATA et al., 2003). VP4 and VP7 elicit neutralizing antibody responses and form the basis of the current dual classification of group A rotavirus into G (standing for glycoprotein VP7) and P (standing for protease-sensitive protein VP4) serotypes. As the VP7 and VP4 genes segregate independently, various combinations of G and P types have been detected in natural isolates. At least 14 and 20 different G and P types have been identified, respectively. Of those, at least 10 G types and 11 P types have been found to infect humans (SÁNCHES-FAUQUIER et al., 2004). Serotyping by ELISA with anti-VP7 serotype-specific monoclonal antibodies and

genotyping by reverse transcription-PCR (RT-PCR) has been widely used for typing (SÁNCHES-FAUQUIER et al., 2004).

Epidemiological and molecular studies in many countries show complex patterns of change from year to year in the serotypes and electropherotypes that cause diarrhea in hospitalized children from the same geographical areas. To date, the majority of severe disease worldwide has been caused by serotypes G1, G2, G3, G4, and P1A (genotype P) (FRÜHWIRTH et al., 2001) and serotype P1B (genotype P) (LINHARES, 2000). Recent epidemiological studies in Bangladesh, Brazil, India, Kenya, and the United States show that other G and P types (G5, G6, G8, G9, G10, P2A, P8) (SANEKATA et al., 2003; LYNCH et al., 2001) can be common and may be of emerging importance in some communities. There is great genetic diversity within each G and P type on the basis of the gel electrophoretic analysis of gene patterns (electropherotypes) (BISHOP et al., 2001).

Rotaviruses A constitute the most important cause of severe gastroenteritis among infants and young children in developing and developed countries (SÁNCHES-FAUQUIER et al., 2004; SANEKATA et al., 2003; BISHOP et al., 2001; MASCARENHAS et al., 2002). Group A rotavirus causes diarrhea in infants and has been detected in many countries since 1973. On the other hand, group B rotavirus was found in China in 1983. This virus is responsible predominantly for adult diarrhea and causes cholera-like diarrhea in adults, infecting more than a million people in a single epidemic (SANEKATA et al., 2003).

The initial steps in a viral infection involve the specific attachment of the viral particle to a receptor(s) on the cell surface, followed by internalization of the virus into the cell and the subsequent uncoating of the virion to release the active transcription complex. These events are essential for the successful initiation of a virus replication cycle and play an important role in the tissue tropism and pathogenesis of viruses. In general, viruses can enter cells by fusion of the viral and cellular membranes at the plasma membrane level or in endocytic vesicles or, more rarely, in the case of nonenveloped viruses, by a direct mechanism at the cell surface by which the viral particles are directly translocated into the cytoplasm. The endocytic pathways used by different viruses include clathrin-mediated endocytosis, uptake via caveolae, macropinocytosis, phagocytosis, and a novel nonclathrin, noncaveolar pathway that is currently not well characterized. (SAN MARTÍN et al., 2004).

The rate of the entry step is increased by, and most probably dependent on, trypsin treatment of the virus, which cleaves VP4 into two polypeptides, VP8 and VP5. The cleavage of VP4 does not affect cell binding and has been associated with entry of the virus by direct cell membrane penetration (SAN MARTÍN et al., 2004).

In vivo, rotavirus exhibits a marked tropism for the differentiated enterocytes of the intestinal epithelium. In vitro, differentiated, and undifferentiated intestinal cells can be infected. Was observed that rotavirus infection of the human intestinal epithelial Caco-2 cells induces cytoskeleton alterations as a function of cell differentiation (BRUNET et al., 2000).

The toxin NSP4 is suspected of initiating the secretorial diarrhea, through the activation of the enteric nervous system, collaborating indirectly in the synthesis of others active biological compounds (mediators) or neuromodutators in inflammatory cells or endocrine intestine cells (RODRIGUES et al., 2004).

Unfortunately, the circulating rotavirus strain(s) have not been characterized where outbreaks have been reported. We know little about why adults developed rotavirus diarrhea when they should have had immunity from multiple previous natural exposures in childhood. Some studies demonstrate that group A rotavirus can cause epidemic gastroenteritis in adults and in elderly individuals and that, when it does, genotype G2 strains are likely to be involved. Therefore, reference laboratories should consider rotavirus as a possible causative agent for outbreaks of diarrhea in adults (GRIFFIN et al., 2002).

EPIDEMIOLOGY

Worldwide, rotaviruses account for 440,000 deaths per year among infants and young children. Each year, rotavirus causes an estimated 111 million episodes of diarrhea requiring only home care, 25 million clinic visits, 2 million hospitalizations and 352,000–592,000 deaths (median 440,000 deaths) in children <5 years of age. In other words, by 5 years of age, almost all children will have an episode of rotavirus gastroenteritis, 1 in 5 will require a clinic visit, 1 in 65 will require hospitalization, and approximately 1 in 293 will die (PARASHAR et al., 2003).

In Brazil, rotaviruses were first seen in 1976 by scanning electron microscopy of stool samples from diarrheic infants in Belém, Pará. Hospital-based studies have shown that rotaviruses are associated with 12-42% of cases of acute diarrhea. In addition, community-based studies yielded an average of 0.25 rotavirus-related diarrheal episodes per child per year. The first investigations about gastroenteritis caused by rotavirus in Latin America were made in the seventy's, few years after the discovery of this enteropathogen by Bishop. Along two decades, multiple infection aspects presented by these

viruses have been studied in national ambit, including since the first findings of the electronic microscopy to molecular characterization of circulating strain(s) and clinical trials with experimental vaccines. Several studies were made in Brazilian territory, and they englobed different regions of the country. Based on them, multiple rates were determined relating to rotaviruses diarrhea among children less than six years old. It has been shown that over 70% of children develop rotavirus antibodies by the age of 4-5 years. Generally, the available data indicates that at least 2/3 of rotaviruses diarrhea happens among 6 and 24 months. In general terms, the rotaviruses diarrhea frequency varied from 12% to 42%. The regional positivity rates are, in average, 36,5% in North, 25%, 24%, 22% and 42%, in Northeast, Middle West, Southeast and South, respectively. Most of the investigation was made in the ambulatory or hospital, so it can be inferred that great part of the situations were clinically more serious. Although there is a number of information concerning rotaviruses gastroenteritis in the country, the nowadays epidemiological peculiarities imposes the establishment of a large laboratorial net with the purpose of systematic vigilance of prevalent viral samples (LINHARES, 2000).

The seasonal distribution of rotaviruses gastroenteritis in Brazil follows the patterns registered in tropical and temperate regions of the planet. Therefore, Brazilian Middle East, Southeast and South show larger incidence in the drier months of the year (may to september); despite that, north and northeast didn't show such seasonality (LINHARES, 2000).

Outbreaks in Brazil of gastroenteritis by rotaviruses are not so frequent. Most cases are restricted to places with human crowds, as schools, daycare, hospital, nursery and even in the families (LINHARES,2000).

It was observed that the major clinical expression of diarrhea is caused by rotaviruses, if compared with diarrhea caused by other pathogens, in the community or in the hospital. The clinical-epidemiological investigations lead until today support seriousness of the gastroenteritis caused by rotaviruses (LINHARES,2000).

There are four known universal epidemiological important serotypes [G (from glycoprotein) 1,G2, G3 e G4] occurring in Brazil. The severe type of diarrhecal episodes associated with rotaviruses is known universally, causing most impact in Third World countries, where there are worsening factors such as desnutrition and multiple infections involving others enteropathogens (LINHARES,2000).

Rotavirus is the most common cause of severe diarrhea in children worldwide. More than 90% of children are infected with rotavirus by 3 years of age. Whereas first infections in infants >3 months of age are associated with diarrhea, subsequent infections are generally milder or asymptomatic. In fact, subclinical rotavirus infections are very common among adults. Rotavirus diarrhea has been reported in parents and caretakers of children with rotavirus diarrhea, in elderly residents of hospital wards and long-term care institutions, in travelers, and in persons of all ages who live in isolated communities. Unfortunately, the circulating rotavirus strain(s) have not been characterized where these outbreaks have been reported (GRIFFIN et al., 2002).

The classic clinical findings are the sudden beginning of high fever (LINHARES,2000; ORLANDI et al 2001) and vomiting, followed by severe diarrhea. Frequently there is isotonic dehydration, in some cases leading to death. The main clinical expressions are liquid evacuations, vomiting, nausea, abdominal cramps and fever in infected children in the community. In hospitals the clinical parameters are fever, vomiting and dehydration (LINHARES,2000).

Rotavirus is the primary cause of severe gastroenteritis in children. Infection is localized in the intestine, and only rare reports suggest any morbidity resulting from extraintestinal involvement. Recently, however, a number of investigators have reported CNS (Central Nervous System) complications in association with rotavirus infections. Patients with rotavirus diarrhea and benign or severe convulsions, or encephalitis have been found to have evidence of rotavirus in the CSF (cerebrospinal fluid). However, the significance of this finding is unclear. The presence of rotavirus in CSF could be explained as either a cause of convulsions, contamination of CSF by fecal material introduced during lumbar puncture or in the testing laboratory, or carriage of rotavirus RNA in trafficking lymphocytes (LYNCH et al., 2001).

The advent of electronic microscopy and, consequently, imunoenzimatic procedure (ELISA), proportioned the rotaviruses finding in fecal samples. The virological study of fecal samples has to be conserved in 4o C during 24-48h to be analyzed and subsequently in –80o C aliquot (RIECHMANN et al., 2004).

Generally, the process is established from acute diarrheal episode involving children. The subclinical and asymptomatic infections among adults are common and only one viral strain is involved (LINHARES et al., 2000).

The detection of rotavirus is made by various methods, including EIA, immune electron microscopy, electron microscopy, and RT-PCR11. The ELISA test has to be performed according to the manufacturer's protocol immediately after collection of the first sample. The sensitivity of this test was 95% and the specificity 90%

(FRÜHWIRTH et al., 2001).

PREVENTION AND TREATMENT

Despite improved treatment of diarrhea, this disease has not been controlled yet8. The routine use of Oral Rehydration Salts in Brazil is seen as a highly efficient method and with large acceptation against acute diarrhea (LINHARES et al., 2000).

It is agreed, nowadays, that the effective control of rotaviruses gastroenteritis will be provided by an effective vaccine to the current use along the first semester of life. Such affirmative is given because of the singular epidemiologic of this viruses infections, causing similar incidence rates in developed countries and countries in development. It is deduced, therefore, that health public measures, as access to potable water and basic sanitation improvement, will result in inexpressive impact in the morbidity associated with rotaviruses diarrhea (LINHARES et al., 2000).

Despite that, rotaviruses are excreted in very large quantities in the feces of infected subjects, at a rate of up to 1011 virus particles per gram. Very resistant in the environment, they are therefore present in large amounts in wastewater and generally in environmental water. Their physicochemical characteristics lead us to suspect that certain treatments of water for human consumption may not be completely effective. Several studies have mentioned the presence of rotaviruses in drinking water or the occurrence of epidemics originating from contaminated water. In parallel with interhuman contamination, drinking water might thus play a role in the occurrence of sporadic cases (GRATACAP-CAVALLIER et al., 2000).

Development of rotavirus vaccines has been a high priority, and recent efforts have led to the licensure of a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) (BERNSTEIN et al., 2002). The first evaluation of the vaccine "candidate" against rotaviruses in Brazil happened in the first half of the ninety's, in Belém, Pará. The used immunizer was RRV-TV, desenvolved in the National Institute of Health, Bethesda, Maryland, EUA. This vaccine groups together four different attenuated strains. The product, designed Rotashield, deserved a license from Food and Drug Administration (FDA), EUA, in 1998 august, for oral routine use, three doses (2, 4 e 6 months), in that country. The vaccine scheme, in 2, 4 and 6 months, was proposed because of the good chances of concomitant administration with antipolio. This represents advantageous aspects if the vaccine was to be incorporated in the basic immunization calendar in Brazil. RRV-TV conferred 35% protection according to a two-year follow-up study in Belém, Pará, Brazil, but reached an efficacy of 60% during the first year of life. RRV-TV was also shown to be 75% protective against very severe gastroenteritis in northern Brazil. A limiting factor to the vaccine utilization, however, is its elevated cost, estimated in U$ 30.00 per dose (LINHARES, 2000). Furthermore, the use of live oral vaccine was discontinued, and the vaccine withdrawn from the US market, following the occurrence of intussusception among vaccinated children (LINHARES, 2000; FRÜHWIRTH et al., 2001; MASCARENHAS et al., 2002).

As alternatives to Rotashield arise, presently, two promising vaccine "candidates" against rotaviruses. The first, human rotavirus vaccine 89-12, recently has been shown to be safe and effective, in a small efficacy trial. The equivalent-to-superior efficacy of human rotavirus vaccine 89-12 compared with RRV-TV has led to expanded evaluation, in several countries, of a vaccine derived from strain 89-12. The main issues to be determined in ongoing trials are the safety of the vaccine, including its relationship to intussusception, and the protection provided against nonserotype G1 rotavirus strains (BERNSTEIN et al., 2002).

There is, also, another genetically restructured preparation, using human and bovine strains. However, an eventual current use of these immunizers needs at least 6 to 7 years of investigations, since the available results reflect early stages of evaluation (LINHARES,2000).

As long as rotaviruses infection data are multiple, especially the ones about hospital situation, there is the need for the establishment of a national net with the purpose of systematic epidemiological vigilance. The analysis of the disease impact in the country, to characterize it with precision and representativity, would only be possible with the introduction of a patterned protocol, accentuating morbidity and mortality aspects (LINHARES,2000). There is, therefore, urgent need for national intervention programs based on reliable epidemiological data (FRÜHWIRTH et al., 2001).

FINAL COMENTS

After two decades of epidemiological studies about rotaviruses infections in Brazil, the indicators are clear concerning relevance assumed by this agents in the beginning of the acute infant gastroenteritis, specially the severe ones (LINHARES, 2000).

The establishment of regional networks for rotavirus surveillance in sentinel hospitals will facilitate more timely and refined estimates of disease illness and death. These data, along with information on illness and

costs of rotavirus infections, will assist policy makers in assessing the magnitude of the problem of rotavirus in their own setting and in setting priorities for interventions, such as the next generation of rotavirus vaccines, which may be available in the near future (PARASHAR et al., 2003).

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