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Research Article

Molecular Epidemiology and Clinical Risk Factors of Rotavirus Diarrhea: Single Center 5-Year Experience

Rotavirüs İshalinin Moleküler Epidemiyolojisi ve Klinik Risk Faktörleri: 5 Yıllık Tek Merkez Deneyim

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ABSTRACT

Objective: *Acute gastroenteritis due to the rotavirus is one of the common causes of morbidity and mortality in children under five years of age. The objective of this study was to evaluate the epidemiological, clinical, and laboratory data of rotavirus diarrhea in hospitalized children under five years of age.*
Methods: *All children between one month and 60 months old ages who were hospitalized in Health Sciences University Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital during September 2013 to August 2017 and diagnosed as acute gastroenteritis with rotavirus antigen test positive in feces were included in the current study. Data of the patients were collected retrospectively from medical records.*
Results: *A total of 100 patients were evaluated.The median age of the patients was 13 months (IQR 5-45 months) and 54 patients were male and 46 were female.The highest hospitalization rate was in December, followed by November, and in October. The most common type of G9P (8) serotype was detected in rotavirus serotype analysis by PCR. Breastfeeding infants had milder clinic findings in comparison to the older ones. It was found that clinical findings were milder and Vesicari score was lower in infants who had breast milk. Vesikari score was found to be high in children with severe clinical findings.*
Conclusion: *Rotavirus infection is important for all ages.In case of fever, increased numbers of vomiting and diarrhea, and higher Vesikari system scores may be associated with the severe clinical forms. Determination of rotavirus serotypes and clinical monitoring of genotypic changes are required.*

Keywords: *Gastroenteritis, rotavirus, rotavirus serotype, Vesikari score*

ÖZ

Amaç: *Rotavirüs gastroenteriti tüm dünyada, beş yaş altı çocuklarda önemli morbidite ve mortalite nedenidir. Bu çalışma ile rotavirüs ishali nedeni ile hastaneye yatan beş yaş altı çocukların epidemiyolojik özelliklerinin, klinik ve laboratuvar verilerinin değerlendirilmesi amaçlandı.*
Yöntem: *Sağlık Bilimleri Üniversitesi Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi'ne Eylül 2013 - Ağustos 2017 tarihleri arasında akut ishal nedeni ile yatırılan ve dışkısında rotavirüs antijeni pozitif saptanan 1 ay - 60 ay aralığındaki hastalar çalışmaya dahil edildi. Hastaların verileri, geriye dönük olarak "hasta yatış dosyaları" ve "hastane elektronik bilgi sistemi" kullanılarak elde edildi.*
Bulgular: *Çalışmada toplam 100 hasta değerlendirildi. Medyan yaş 13 ay (IQR 5-45 ay) ve 54'ü erkek, 46'sı kızdı. En sık yatış Aralık ayında yapılmış, bunu Kasım ve Ekim ayları takip etmiştir. PCR ile bakılan rotavirüs serotip analizinde en sık G9P(8) serotipi saptandı. Anne sütü alan bebeklerde klinik bulguların daha hafif olduğu ve vesikari skorunun daha düşük olduğu saptandı. Ağır klinik bulguları olan çocuklarda da Vesikari skorunun yüksek olduğu bulundu.*
Sonuç: *Rotavirüs enfeksiyonu,anne sütü alan bebeklerde daha hafif klinik bulgulara neden olmaktadır. Başvuru sırasında Vesikari skoru ciddi hastalığı ön görmede etkili olabilir. Rotavirüs serotiplerinin belirlenmesi ve genotipik değişimlerin klinik olarak izlenmesi gereklidir.*

Anahtar kelimeler: *Gastroenterit, rotavirüs, rotavirüs serotip, Vesikari skoru*

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INTRODUCTION

Rotavirus associated with diarrhea is the most common cause of mortality and morbidity in children under 5 years of age worldwide. In United States, there are 55,000-70,000 hospitalizations each year due to rotavirus diarrhea [1,2]. In a report published between 2000 and 2013 on rotavirus, it was stated that the number of deaths with rotavirus gastroenteritis under the age of 5 was 529,000, 215.000 in 2013 [1]. By the studies conducted in different countries, it has been reported that rotavirus is the agent in 10-70% of viral gastroenteritis cases [2].

Rotavirus is a double-stranded ribonucleic acid (RNA) virus and divided into 7 serogroups from A to G (9). The most common rotavirus types in the world are G1P[8], G3P[8], G4P[8] and G2P[4], and G9P[8]. The frequency of these five strains makes up more than 90% of the strains compared to the other strains. The dominant serotypes vary from year to year and from region to region [11].

Rotavirus infections are more common in winter and spring in studies [3]. Sudden-onset watery diarrhea is followed by vomiting, which usually lasts 1-3 days. Diarrhea, which can occur 10-20 times a day, can last 5-7 days. It can cause severe dehydration, especially in children younger than 2 years old. It has been reported that the severity and duration of the disease are low in children fed with breast milk [5].

Altough the rotavirus associated diarhea has a usually self-limiting milder course, it may cause severe syptoms aspecially in infants. A scoring system was developed to determine the course of the disease and the treatment approach. Parameters used in clinical scoring; The number of daily diarrhea, the number of daily vomiting, the number of days for vomiting, the highest degree of fever, the degree of dehydration, and treatment requirements are included [7].

In this study, the clinical, laboratory, and epidemiological characteristics of children under the age of five who were hospitalized for rotavirus gastroenteritis between 2013-2017 were examined.

MATERIAL and METHODS

Patients between the ages of 1 month and 60 months who were hospitalized in the **** Hospital due to acute diarrhea between September 2013 and May 2017 and who were found to have positive rotavirus antigen in their stool were included in the study. The study was initiated after it was approved by the Ethics Committee of our hospital (2017/17-06).

The data of the patients were recorded retrospectively in the case report form using “patient admission files” and “hospital electronic information system”. Patients whose diarrhea complaint lasted longer than 14 days were accepted as “prolonged diarrhea” and excluded from the study. Besides, patients over the age of five and under onemonth, patients with chronic diseases associated with the gastrointestinal system, immune system disorders, and patients whose rotavirus antigen test was found to be positive, were not included in the study.

A qualitative immunochromatographic assay test (Ameritek Inc, Everett, WA, USA), which is a rapid antigen test, was used to detect rotavirus antigen in stool. This examination was carried out in the microbiology laboratory of our hospital following the test procedure recommended by the manufacturer. After the stool sample was treated with 1 mL of buffer solution, approximately 150 microL of the mixture was dropped onto the strip in the kit. Waiting for 10 minutes, the reaction of the liquid was evaluated. The sensitivity of the test was 98,9% and the specificity was 99,6% [13].

The age, gender, number of days of hospitalization, month and season of hospitalization, breastfeeding history, previous antibiotic use, and complications developed during the follow-up of the patients with positive rotavirus antigen in stool samples were recorded. Vital signs, body weight, and dehydration degrees of the patients at admission were also recorded. Dehydration due to rotavirus gastroenteritis is classified as mild, moderate and severe [14].

The rotavirus diarrhea clinical severity score was applied to all patients. Clinical findings were scored between “0-20 points”. Parameters used in clinical

scoring; It includes the number of daily diarrhea, the number of daily vomiting, how many days it has been vomiting, the highest fever, the degree of dehydration, and treatment requirements (Table 1).

According to this scoring system, those who scored <7 points were considered mild, 7-10 points moderate, and 11 points as severe disease. The patients were divided into two groups according to their breastfeeding and not breastfeeding at the time of admission and compared in terms of Vesikari score, presence of vomiting, duration of diarrhea, length of stay, presence of fever, and dehydration.

Within the framework of the Central Laboratory surveillance program; The rotavirus genotypes were determined by sending stool samples of rotavirus positive patients. The frequency distribution of genotyped patients was made according to months and seasons. Statistical analysis of the data obtained as a result of the study was performed using the SPSS 24 (Statistical Package for the Social Sciences, Chicago, IL, USA) program. Chi-square test, Mann Whitney-U test, and median tests were used for demographic data. The Kruskal Wallis test (ANOVA) was used to evaluate whether there was any difference between the determined rotavirus genotypes in terms of clinical score, length of stay, season distribution, and duration of diarrhea. Average ages were given in months. Results are given as n (%) or mean±standard deviation (SD) (lower-upper value). p<0,05 was considered statistically significant.

Table 1. The rotavirus diarrhea clinical severity score.

	Vesikari Score		
Parameters	**1**	**2**	**3**
Maximum Number Stools per Day	1-3	4-5	≥6
Diarrhea Duration (Days)	1-4	5	≥6
Maximum Number Vomiting Episodes per Day	1-2	2-4	≥5
Vomiting Duration (Days)	1	2	≥3
Temperature (C^0)	37.1-38.4	38.5-38.9	≥39
Dehydration	Normal or light	1-5%	≥6%
Treatment	Rehydration	Hospitalization	Dehydration despite treatment

RESULTS

A total of 100 patients were evaluated in the study. Of these, 54 (54%) were male and 46 (46%) were female. The median age of the patients was 13 months (IQR 5-45 months). When the distribution of patients hospitalized due to rotavirus gastroenteritis by months was examined, it was observed that the most frequent hospitalizations were made in

December (n=17, 17%), followed by November

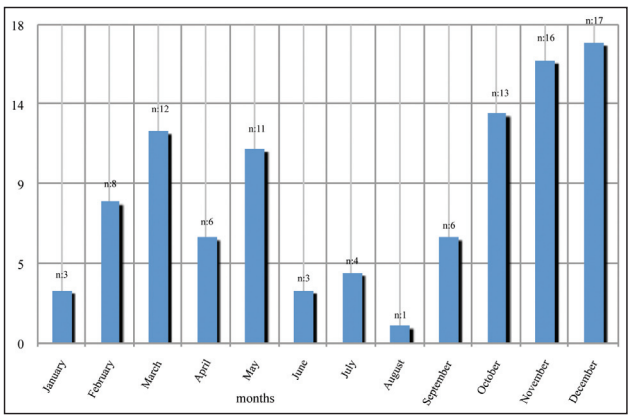

Figure 1. Distribution of patients hospitalized due to rotavirus gastroenteritis by months.

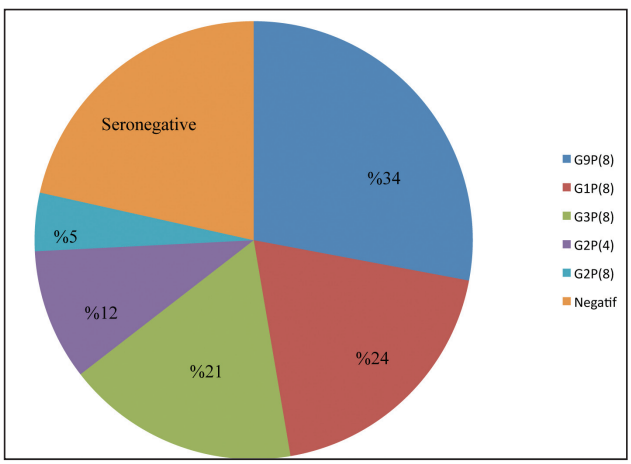

Figure 2. Distribution of PCR-detected serotypes in patients with positive rotavirus antigen .

(n=16, 16%) and October (n=13, 13%). Distrubition of the patients were shown in Figure 1.

Most frequently detected serotypes were G9P (n=26, 34%), G1P (n=18, 30%), and G3P (8) (n=16, 24%). In 20 (20%) patients, although rotavirus antigen was found to be positive in the stool, no serotype was detected by RT-PCR. Serotypes detected by PCR are shown in Figure 2. There was no statistically differences between the detected serotypes and clinical findings, duration of symptoms, and severity of the course (p>0.05).

When the patients who took breast milk and those who did not were compared, no statistically significant difference was found in terms of the presence of vomiting (p=0.069), duration of diarrhea (p=0.143), or length of stay (p=0.417). However, it was found that the frequency of fever was higher and the degree of dehydration was more severe in those who did not breastfeed (p=0.038 and p=0.025, respectively). It was found that among inpatients with positive rotavirus, Vesikari scores at the time of admission were higher than those who received breast milk, and there was a statistically significant difference (p=0.001).

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Vesikari scores of patients admitted to the intensive care unit; It was statistically higher than patients who were not hospitalized in intensive care (p=0.001). There was no statistically significant difference in patients in the mild and moderate disease groups according to the vesikari classification.

Table 2. The degree of dehydration and Vesikari skore according to their breast milk intake.

Dehydration	Breastfeeding (n=41)	Not Breastfeeding (n=59)	P-value
Mild dehydration n (%)	27 (65.8%)	29 (49.2%)	0.025
Moderate dehydration n (%)	14 (34.2%)	22 (37.2%)	
Severe dehydration n (%)	0 (0.0%)	8 (13.6%)	
Vesikari skore mean (±sd)	8.4±2.0	9.9±2.1	0.001

DISCUSSION

Acute gastroenteritis is one of the most important causes of mortality and morbidity in the world, especially in developing countries. In prevalence studies conducted in different parts of the world, the frequency of rotavirus varies and it is reported that rotavirus is the agent in 10-70% of viral gastroenteritis cases [1,2,9,15,19]. In previous studies, it has been reported that rotavirus diarrhea is most common in children between the ages of 6 and 24 months, and it peaks at 9-12 months [20]. The median age of the patients in our study was 13 months. Although these values are similar to the literature, 69% of the patients were children older than 24 months. These results can only be due to the evaluation of inpatients. Indeed, in a large-scale study in which rotavirus surveillance in our country was tried to be determined, it was shown that rotavirus gastroenteritis was more common in children aged 13 to 24 months, and this age group was followed by children between 25 and 36 months [21]. It has been reported that rotavirus infection shifts to older ages, especially in developed countries [20,21].

It is thought to be due to the increase in the average age, virus genotype changes, and the provision of hygiene conditions. Rotavirus is more common in cold seasons. The frequency of rotavirus in America and Europe increases in the period of December-March, while in Africa, the frequency of rotavirus was higher in dry seasons [22]. In our country, it has been reported that rotavirus gastroenteritis cases are frequently seen between September and May [23,24]. In our study, it was observed that hospitalizations due to rotavirus gastroenteritis were more frequent in November and December, and seasonally, most frequently in autumn.

Rotavirus can cause serious and life-threatening dehydration accompanied by vomiting [25]. Fluid electrolyte loss, metabolic acidosis, nutritional deficiency, malnutrition, and dermatitis seen in acute gastroenteritis are also common in rotavirus infection. It may cause severe dehydration, especially in children younger than 2 years old [25,26]. In a study

conducted in Africa, dehydration was reported to be more severe in the rotavirus positive group [27]. In our study, mild dehydration was found in 28%, moderate dehydration in 64%, and severe dehydration in 8% of the patients hospitalized due to rotavirus gastroenteritis. It was noted that 19 (19%) of the patients in our study received antibiotic treatment during their hospitalization, and 17 of these patients started treatment with a pre-diagnosis of respiratory tract infection. Similarly, in a study conducted in Mexico, it was reported that antibiotics were used at a rate of 17.6% in patients with rotavirus positive gastroenteritis [28]. Apart from fever and symptoms related to the gastrointestinal system, it can also lead to respiratory tract-related symptoms associated with rotavirus infection. Studies are reporting that 30-50% of the cases have respiratory tract symptoms, cough and nasal discharge are common [29,30].

It is a matter of debate whether this is due to the factor or to the viruses that affect the accompanying respiratory tract since the time of its occurrence is mostly in the winter months. Diagnosis of rotavirus gastroenteritis is generally indistinguishable from other gastroenteritis by physical examination and clinical findings. Since the treatment of rotavirus gastroenteritis is hydration and supportive therapy like other viral gastroenteritis, specific microbiological diagnosis is not necessary in most cases. However, in the case of prolonged diarrhea, patients with the suppressed immune system, severe chronic diseases, and in surveillance studies, rotavirus can be examined as an etiological agent. Definitive diagnosis may also prevent the use of unnecessary and potentially harmful antibiotics in rotavirus gastroenteritis [31]. It is known that most physicians cannot determine whether there is rotavirus infection at the beginning of the clinic, and therefore, antibiotic treatment is started considering other diagnoses [32]. Many scoring systems have been established to determine the course and treatment approach of acute gastroenteritis. The most used scoring is Vesikari scoring [7]. In a cohort study, Vesikari score was reported to be related in terms of dehydration and treatment duration [33]. In our study, the median value of the Vesikari score of the patients was determined to be 9,2. According to the degree of Vesikari, 35% of the cases were evaluated as mild, 57% as moderate, and 8% as a serious disease. Within the framework of different studies, it was observed that Vesikari scoring was more significant in outpatients [34]. In our study, the median value of Vesikari score of 7 (7%) patients hospitalized in the intensive care unit was 14 points, and we found statistically significantly higher. Therefore, it has been observed that the Vesikari score can also be used in severely ill patients.

Monitoring of serotypes is important in terms of the development of rotavirus infection and vaccine studies. Rotavirus serotypes differ by region. The most common serotypes in acute gastroenteritis caused by group A rotaviruses in the world are G1P(8), G2P(4), G3P(8), G4P(8), G9P(8) [35]. In a study conducted in our country in 2014, the most common G9 genotype (48%) was found, followed by G1 (25.9%), G2 (16.2%) and G3 (4.3%) [21]. In another study conducted between 2014 and 2016, 1396 RT-PCR detected the most common G1 (28.3%), followed by G3 (21%), G9 (18.8%), G2 (16.3%) [36]. While the prevalence of G9P(8) serotype was 2-10% in prevalence studies conducted in India between 2003 and 2007, it reached 40% in the prevalence studies conducted in 2013 [37]. In our study, we found G9P(8) with a frequency of 32,5% [26] as the most common serotype in patients. Then, 22,5% [18] G1P(8), 20% [16] G3P(8) followed. The types of virus serotypes in terms of frequency vary from country to country and from year to year. The most common serotype G9P(8) in our study is increasing in epidemiological studies conducted worldwide. It is the most common serotype in many studies. These findings support our study. It is necessary to determine virus serotypes and to monitor genotypic changes. Besides, it is important for which serotypes in the country for the use of the vaccine to be developed. The relationship between rotavirus serotypes in terms of the severity of the infection has not been established. In a study conducted in India, Vesikari scoring of G9 serotypes was found higher than G1 serotypes [38]. In another study, it was reported that the G2P(4) serotype caused a more severe clinical picture [39]. In our study,

we performed Vesikari scoring on our patients to investigate whether there is a difference in clinical severity of rotavirus serotypes. We found no significant difference in terms of the clinical severity of the disease.

Rotavirus, outside the intestine; has been detected in extraintestinal tissues such as the liver, heart, lung, and central nervous system. In our study, hypovolemic shock in 2 (2%) patients, acute renal failure secondary to dehydration in 3 (3%) patients, septic shock in 2 (2%), metabolic acidosis in 6 (6%) patients, increased liver function test in 5 (5%) patients, 4 (4%) patients had hyponatremia, 6 (6%) patients had hypernatremia, and 19 (19%) patients had respiratory tract infection. 7 (7%) patients were followed up in the intensive care unit.

Vesikari score was higher in patients with severe disease. Therefore, we determined that the vesikari score could be used in severe patients in terms of predicting the severity of the disease.The main principle in treatment is to replace lost fluid and electrolytes. There is no specific antiviral therapy. Rotavirus infections in infants younger than 4-6 months are often asymptomatic due to the protective effect of maternal antibodies. It is symptomatic in only 10-20% of cases and is usually mild. However, serious infections may be seen in premature babies. It has been reported that breastfeeding reduces the risk of rotavirus gastroenteritis [44]. We found that the frequency of fever and dehydration was more severe in patients with rotavirus gastroenteritis compared to patients who did not take breast milk. Besides, we found higher Vesikari scores in patients who did not receive breast milk. It has been observed that breastfeeding is protective in rotavirus gastroenteritis and the clinical course is milder, and breast milk intake should be encouraged in patients who can be fed orally in rotavirus diarrhea. The major limitation of the study was that it has been planned retrospectively. Since the data in our study were analyzed retrospectively, instant clinical data and outcomes were not included.

CONCLUSION

Our study shows the 5-year surveillance of rotavirus genotypes and is also important in terms of including the broad clinical features of rotavirus diarrhea.

Ethics Committee Approval: S.B.U. Izmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital Clinical Research Ethics Committee approval was obtained (2017/17-06).
Conflict of Interest: The authors declared that there were no conflicts of interest.
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Informed Consent: Since our study was retrospective, consent was not obtained from the patients.

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