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ORIGINAL ARTICLE

Demographic, Laboratory Features, and Vaccination Status of Hospitalized Children Under 5 Years Old with Rotavirus Gastroenteritis

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Abstract

Introduction: The aim of this study is to evaluate the demographic and clinical characteristics and vaccination status of patients under 5 years with rotavirus antigen-positive acute gastroenteritis (RVGE).

Methods: Patients diagnosed with RVGE, who were admitted between December 1, 2017, and November 30, 2018, were included in the study. The demographic and laboratory characteristics and the vaccination status of the children were retrospectively evaluated.

Results: Of the 194 patients included in the study, 115 (59.3%) were male and 79 (40.7%) were female. Children who breastfed for less than 6 months had a longer length of hospital stay (LOS) than those who breastfed for 6 months or more (p=0.001). LOS for unvaccinated children was longer than for vaccinated children (p=0.003). Children with blood group A had longer LOS than children with other blood groups. Children with significant stool leukocyte presence had longer LOS than those without stool leukocytes (p=0.013). The complication that significantly increased the LOS was hypokalemia (p=0.042).

Discussion and Conclusion: Vaccination has a protective effect that reduces morbidity in children under 5 years with RVGE. Our study found that both breastfeeding and the rotavirus vaccine significantly reduced the length of hospital stay.

Keywords: Child; Gastroenteritis; Rotavirus; Vaccination.

Rotavirus gastroenteritis (RVGE) is the most common cause of severe diarrhea among children younger than 5 years in both developed and developing countries and contributes to 40% of hospital admissions worldwide[1,2]. Although mortality due to RVGE is rare in developed countries, it causes significant morbidity and economic burden on the healthcare system[3]. Each year, about 111 million episodes of gastroenteritis due to rotavirus (RV) are reported in children worldwide, of whom 2 million require hospitalizations and 400,000 deaths occur[4]. A recent study estimated that there are 3.6 million episodes of rotavirus disease annually among the 23.6 million children under the age of 5, living in the European Union, with 231 deaths, more than 87,000 hospitalizations[5]. In Türkiye, mortality due to diarrheal disease has been significantly reduced since 1986 by the implementation

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of the 'Diarrheal Disease Control Programme'. During this period, diarrheal diseases fell from the second to the seventh cause of pediatric mortality[6]. However, diarrheal disease and its complications are still an important cause of infant morbidity and mortality. Studies conducted on the epidemiology of RVGE in Türkiye found that rotavirus was responsible for 15-40% of diarrheal disease in children under five years of age and approximately 3000 deaths occur annually in Türkiye due to RVGE[7,8].

Although rotavirus infections may occur in every month of the year, there is seasonality to rotavirus infection, with the majority of cases occurring in the winter months between November and February[9,10]. RV is transmitted by fecal–oral contact, droplets in the air, and even a small inoculum is infectious[11]. During the 18-36 hour incubation period, the virus enters the intestinal epithelial cells, where non-structural protein, a powerful enterotoxin that can cause diarrhea, is produced[12].

Clinical manifestations of the disease depend on the infectious dose, local immunity, the state of nutrition, and breastfeeding that protect the infant from rotavirus infection[13]. Although the symptoms of RVGE are vomiting, diarrhea, and fever, it is typically self-limiting, and complete recovery is the norm with adequate hydration[14]. However, it can cause serious complications like hypovolemic shock, dehydration[10], and may even lead to death[15].

Before the introduction of the rotavirus vaccination, nearly every infant was infected with rotavirus at least once[4,12,15]. In 2009, the World Health Organization Strategic Advisory Group of Experts recommended the worldwide inclusion of the rotavirus vaccine in national immunization programs (NIPs), particularly in African and Asian countries[2]. Rotavirus vaccination has not been included in Türkiye's NIP; consequently, guardians have to pay out of pocket for vaccination. Implementation of vaccination into NIP would be expected to reduce the disease burden.

The aim of our study was primarily to gain a better understanding of the epidemiology of RVGE, seasonal and monthly distribution, clinical characteristics, and secondarily to determine the risk factors for the length of hospital stay (LOS). Also, we evaluated the frequency of vaccination in hospitalized children due to RVGE to show whether vaccination has an effect on the LOS. By evaluating the demographic characteristics and vaccination status of children with RVGE under 5 years of age, it is aimed to identify ways to prevent disease progression and reduce its morbidity and mortality.

Materials and Methods

Study Settings and Participants

This retrospective study was conducted at Haydarpaşa Numune Training and Research Hospital, between December 1, 2017, and November 30, 2018. During this period, children aged between 1 month and 5 years who had been hospitalized with a diagnosis of acute gastroenteritis (AGE) were analyzed for eligibility, and those with RV antigen positivity (detected in stool samples) were included in the study. The study was carried out in compliance with the Helsinki Declaration and was approved by the Ethical Committee of the University of Health Sciences (#167, dated 22.02.18).

Exclusion Criteria

1. Children with chronic diarrhea or any chronic disease.
2. Malnutrition.
3. Immunodeficiency.

Demographic, Clinical, and Laboratory Data

The demographic and disease-related information of the patients were collected retrospectively from the medical files of patients, including clinical and laboratory information and vaccination history to determine if any dose of rotavirus vaccines was given. Data including age, gender, breastfeeding duration, season of admittance, blood group, hospital length of stay (LOS), underlying medical conditions, complete blood count, biochemistry, and acute-phase reactant (C-Reactive Protein) stool examination results were extracted from patient charts and electronic hospital records. All biochemical markers and C-reactive protein levels were measured by Abbott-ci 4400. Normal reference values for CRP were 0-0.5 mg/dL, for Na: 135-145 mEq/L, for K: 3.5-4.5 mEq/L, for creatinine: 0.2-0.4 mg/dL for ages 0-2, and 0.4-0.7 mg/dL for ages 2-5. A high Cl value was accepted as a level >111 mEq/L and a high BUN level was considered as >22 mg/dL.

Rotavirus antigen test results in fresh stool specimens were analyzed by quick identification tests for rotavirus (CerTest; Biotec, Zaragoza, Spain). A 4-5 gram stool sample, free from urine contamination, was collected from each study participant within 24 hours of hospital admission.

Statistical Analysis

The data were analyzed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). The expression n(%) was used for categorical variables,

mean±SD for continuous variables showing normal distribution, and when normal distribution was not seen, the median (lower–upper limit) was used. The Mann-Whitney U test was used in the comparison of two groups of data that did not show normal distribution. The Kruskal-Wallis test was used for comparisons of groups of three or more that did not show normal distribution, and the Bonferroni Dunn test was used for pairwise comparisons. Spearman's Correlation Analysis was used to evaluate the relationships between variables that did not show normal distribution. As a multivariate analysis, Linear Regression Analysis was used to evaluate the risk factors on the length of hospital stay. The level of significance was set at $p<0.05$ for all statistical analyses.

Results

During the period between December 1, 2017, and November 30, 2018, out of the total 960 Turkish children younger than 5 years admitted to Haydarpaşa Numune Training and Research Hospital with a diagnosis of acute gastroenteritis (AGE), 194 (20.2%) were diagnosed with rotavirus infections (RVGE). Among those, 79 (40.7%) were females and 115 (59.3%) were males. Patients were divided into three age groups, with half of the children between 1-3 years (n=97). The mean age of the 194 patients diagnosed with RVGE was 24.36±16.37 months. The median duration of breastfeeding was 12 months, and the majority received breastfeeding for more than 6 months (78.4%). Thirty-three (17%) patients had been previously vaccinated against rotavirus. 67.5% had blood group A. The median length of hospital stay (LOS) was 3 days (Table 1).

All patients had positive rotavirus antigen in stool examination, 18 patients (9.3%) had leukocytes in direct examination of stool. Electrolyte imbalance was seen in 164 patients in the form of one of the followings; 29 (14.9%) children had hyponatremia, 11 (5.7%) children had hypokalemia, and 124 (63.9%) children had hyperchloremia. BUN and creatinine elevation were seen in 91 children in total (46.9%). 154 (79.4%) patients had high CRP levels (Table 2).

Admissions for rotavirus gastroenteritis showed seasonal differences, with more cases in winter (n=81, 41.8%) followed by spring. Regarding the monthly distribution, our results showed that rotavirus is more prevalent in February and less in October (Fig. 1).

Children less than 1 year had a longer length of hospital stay than children ≥3 years of age (p=0.044) (Table 3). There

Table 1. Demographic and clinical characteristics of patients

Variables	Min-max (median)
[a]Age (months)	
[a]Age (year)	24.36±16.37
2,03±1,36	
Age (year) (n,%)	
< 1year	51 (26.3)
1-3 year	97(50.0)
≥3 years	46(23.7)
Sex; n (%)	
Male	115 (59.3)
Breastfeeding duration(months)	1-48 (12)
< 6 months	42 (21.6)
6-24 months	140 (72.2)
> 24 months	12 (6.2)
*Vaccination status	
Non-vaccinated	161 (83.0)
Fully vaccinated	33 (17.0)
Travel in last 1 month	
No	161 (83.0)
Yes	33 (17.0)
Risky blood group	
No	63 (32.5)
(Blood group A)	
Yes	131 (67.5)
Length of hospital stay (days)	1-10 (3)

* Vaccination for rotavirus; [a]Mean±SD.

Table 2. Laboratory findings of patients with RVGE

Variables	n (%)
Stool leukocytes	
Present	18 (9.3)
Serum Sodium (Na) mEq/L	
Median(IQR)	127-149 (137)
Hyponatremia (< 135)	29 (14.9)
Serum Potassium (K) mEq/L	
Median(IQR)	2.7-5.6 (4.2)
Hypokalemia (<3.5)	11 (5.7)
Serum Clor (Cl) mEq/L	
Median(IQR)	98-198 (108)
Hyperchloremia (>106)	124 (63.9)
Blood Urea level (mg/dl)	
Median(IQR)	2-30 (12)
Uremia (>22)	5 (2.6)
Creatinine level (mg/dl)	
Normal	108 (55.7)
High	86 (44.3)
CRP	
Median (IQR)	0-8.6 (0.3)
High (>0,5)	154 (79.4)

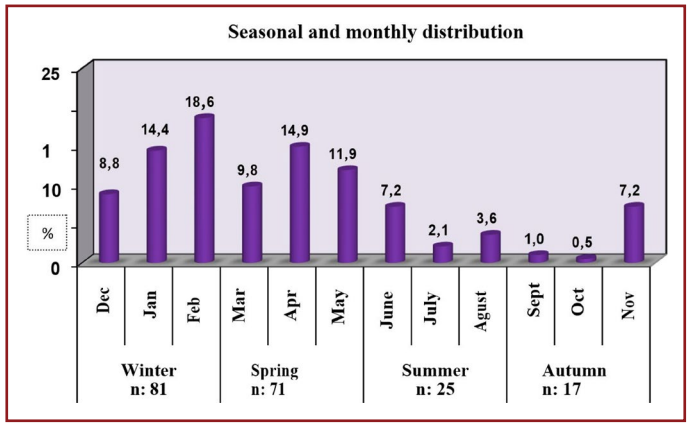

Figure 1. Seasonal and monthly distribution of admission of children with RVGE.

Table 3. Analysis of factors effecting length of hospital stay

Parameters	N	Length of hospital stay (days) Median(IQR)	Mean±SD	p
Age (year)				
<1 year	51	1-10 (3)	3.67±2.26	0.044*
1-3 years	97	1-7 (3)	2.98±1.74	
≥3 years	46	1-10 (2)	2.65±1.84	
Sex				
Female	79	1-10 (3)	3.30±2.14	0.314
Male	115	1-7 (3)	2.93±1.79	
Breastfeeding (mo)				
< 6	42	1-10 (4,5)	4.40±2.27	[b]0.001**
6-24	140	1-7 (2)	2.69±1.68	
> 24	12	1-6 (3)	3.00±1.54	
Vaccination status				
Vaccinated	33	1-7 (1)	2.27±1.74	[a]0.003**
Nonvaccinated	161	1-10 (3)	3.25±1.94	
Travel in last 1 month				
No	161	1-10 (3)	3.00±1.82	[a]0.454
Yes	33	1-10 (3)	3.48±2.43	
Risky Blood group				
Other groups	63	1-7 (2)	2.44±1.64	[a]0.001**
Blood group A	131	1-10 (3)	3.39±2.00	
Stool leukocytes				
None	176	1-10 (3)	2.95±1.83	[a]0.013*
Present	18	1-10 (4)	4.39±2.52	
Serum potassium level				
Normal	183	1-9 (3)	2.99±1.84	[a]0.042*
Hypokalemia	11	2-10 (4)	4.64±2.87	

[a]Mann Whitney U Test, [b]Kruskal Wallis Test, *p<0.05, **p<0.01.

was a negative relationship of 19.4% (r=-0.194; p=0.007) between the children's age and the LOS (the length of stay decreases as the age increases), (Data not shown). A statistically significant relation was found between the LOS and the duration of breastfeeding (p=0.001). A negative correlation was also found (36.3%) between the duration of breastfeeding and the LOS of the children (as the duration of breastfeeding increases, the length of stay decreases), (r=-0.363; p=0.001).

Other statistically significant relations were found between LOS and vaccination status of the children and children with blood group A (p=0.003, p=0.001) (Table 3). Laboratory values of children with RVGE were also analyzed in relation to LOS, and we found children with stool leukocytes and hypokalemia had longer LOS (p=0.013, p=0.042 respectively). Other laboratory values did not give significant results (p>0.05) (Table 3).

The effects of age, breastfeeding, vaccination status, blood group (A), the presence of stool leukocytes, and potassium level, which are among the risk factors affecting the LOS, were evaluated by linear regression analysis. As a result of the analysis, it was seen that age, breastfeeding, vaccination status, blood group (A), the presence of stool leukocytes, and potassium level affected the LOS by 24.8% (R^2=0.248) and the model was statistically significant, (F=10.282, p=0.001). A one-month increase in the age of the children decreased the LOS by 0.023 days (p=0.003) and a one-month increase in breastfeeding decreased the LOS by 0.053 days (p=0.001). The presence of vaccination decreased the LOS by 0.655 days (p=0.048). The presence of A blood group increased the LOS by 0.690 days, the presence of stool leukocytes increased the LOS by 1.18 days and the presence of hypokalemia increased the LOS by 1.57 days (p=0.011, p=0.006, p=0.004) (Table 4).

Discussion

In this retrospective study, we investigated the demographic and clinical features of 194 hospitalized children under 5 years old with acute gastroenteritis (AGE), in which the presence of rotavirus was found to be positive. The majority of the children were under 3 years old (76.3%) and were non-vaccinated (n=161). The most frequent electrolyte imbalance was hyperchloremia (63.9%) followed by hyponatremia (14.9%). Winter and spring were the most common seasons for hospital admissions. Factors that affected the length of hospital stay (LOS) included younger age, breastfeeding duration, vaccination status, blood group A, stool leukocytes, and hypokalemia.

Rotavirus, being the most common viral cause of gastroenteritis, is associated with frequent hospitalizations and deaths among children worldwide[16]. Various

Table 4. Linear regression analysis of factors affecting length of hospital stay

LOS (Days)	Unstandardized Coefficients (B)	%95 CI Lower-Uppper	p
(Constant)	3.753	3.035 - 4.471	0.001**
Age (months)	-0.023	(-0.037) - (-0.008)	0.003**
Breastfeeding (months)	-0.053	(-0.082)-(-0.023)	0.001**
Vaccination status (vaccinated)	-0.655	(-1.305)-(-0.005)	0.048*
Blood group (A)	0.690	0.158-1.221	0.011*
Present stool leukocytes	1.183	0.341-2.026	0.006**
Hypokalemia	1.575	0.519-2.632	0.004**

**p<0, 01, *p<0,05; LOS: length of hospital stay.

studies investigating clinical and demographic features of patients with AGE found that viruses were more frequently identified than bacteria in the etiology; rotavirus being the most common viral infectious agent[17,18]. Jin et al.,[19] claimed that due to effective rotaviral vaccination, the most common cause of acute pediatric viral gastroenteritis had shifted from rotavirus to norovirus; however, rotavirus remained the most common infectious agent in hospitalized children. This finding was also confirmed by another study in which rotavirus was the major cause of hospitalization for AGE among children under 5 years of age[26]. In a prospective study conducted in five European Union countries in children aged <5 years, rotavirus accounted for 56.2% of all hospitalized AGE cases[20]. In our study, we found that 20.2% of children with AGE had rotavirus in hospitalized children.

As for the age group distribution, RVGE can occur at any age but it is more common in infants and young children, especially those aged 6 months to 2 years[21]. In our study, 97 children were aged 1-3 years and 76.3% were below 3 years, which is similar to several previous reports[22,23]. Retrospective studies from Türkiye found rotavirus as the most frequent pathogen in children aged 2-5 years and under 2 years of age[18,24]. The REVEAL study from European countries found that RVGE ranged from 56.7% to 74.2% of cases of AGE in infants aged 6 to 23 months, and from 18.1% to 31.9% in infants aged <6 months[25]. Breastfeeding may be an important factor in this result as exclusive breastfeeding throughout the first 6 months of infancy is beneficial in the prevention of RVGE[26]. In our study, more than 75% of patients received breastfeeding for >6 months, and therefore, the majority of children with RVGE were above 1 year, owing to the protective effect of breastfeeding in the early 6 months.

Previous studies have found a seasonal pattern for RVGE[17,23,24]. The seasonal variation of microorganisms may be explained by unfavorable conditions for transmission, such as ambient temperature and relative humidity during some months[27]. In developed countries, RVGE appears mostly during the winter and spring seasons[28]. In the current study, we also found a similar seasonal pattern (winter: 41.8%, spring: 36.6%). However, RVGE can have various seasonal periods throughout the year[29].

Laboratory findings in RVGE are usually due to dehydration and include electrolyte imbalance and high urea-creatinine values. Studies have found different results in terms of hyponatremia and hypernatremia in patients with RVGE. Akelma et al.[30] reported that the mean serum sodium level was lower in the rotavirus-positive group than in the rotavirus-negative group in their study. In a study by Aldemir-Kocabaş et al., [31] the frequency of hyponatremia was 23.9%, hypernatremia was 8.3%, and hypokalemia was 8.3%. In another study, 23.5% of the patients had hypernatremic dehydration, while the frequency of hypokalemia and hyponatremia was 17.6% and 14.7%, respectively[11]. In our study, the major electrolyte imbalance was hyperchloremia (63.9%). The frequency of hyponatremia was 14.9%, but the frequency of hypokalemia was lower than in the above studies (5.7%). Considering all these data, we believe that electrolytes should be closely monitored in patients with RVGE. In a study conducted by Azemi et al., [13] 31% of patients with RVGE had a high BUN value, while 28.87% had a high creatinine level. In our study, 2.6% (n=5) had high BUN levels and 44.3% (n=86) had high creatinine levels. A high creatinine level may be important in the follow-up of RVGE. With respect to CRP, it may be elevated in patients with RVGE[32]. In our study, the CRP level was found to be high in the majority of children (79.4%, n=154), and high CRP may guide the diagnosis of RVGE.

It is essential that children receive vaccinations to ensure the induction of protection prior to natural rotavirus infection, as both vaccines are effective in decreasing the severity of the infection[12]. Many developed countries have adopted the rotavirus vaccine as part of their National Immunization Programs (NIPs)[4]. Countries with NIPs for rotavirus have observed dramatic reductions in infant cases[2]. A systematic review reported a 49% to 89% decline in rotavirus-associated hospitalizations among children younger than 5 years within 2 years of vaccine introduction[33]. Although the RV vaccines are administered only to infants, a decrease in hospital admissions due to RV was mostly seen in children of a slightly older age; this may indicate that it has an important protective effect in non-immunized children[34]. The vaccine has been used in Türkiye on a voluntary basis, but not through a more comprehensive, nationally funded program. In our study, 83% of patients were non-vaccinated, and the beneficial effect of rotavirus vaccination in vaccinated children (n=33, 17%) has been demonstrated, as they had shorter LOS. Therefore, we think that implementation of vaccination into the Turkish NIP can prevent serious rotavirus enteritis and thus reduce hospitalization rates.

RVGE is usually self-limited, and patients recover within 4-8 days[35]. In our study, LOS ranged from 1 to 10 days, with a median of 3 days. We believe that the shorter LOS in our children was due to rapid rehydration practices and close follow-up of patients. We evaluated each parameter in relation to LOS and found that children less than 1 year had longer LOS than children aged ≥3 years. Atkinson et al. [36] reported that RVGE can be seen at almost any age, but severe symptoms often occur in children aged 6-24 months, supporting our result.

We also evaluated the effect of laboratory parameters on the LOS and found that children with hypokalemia and stool leukocytes had longer LOS than those with normal values. These results may be related to the severity of the disease. Few studies have evaluated laboratory parameters in RVGE, and none of them have reported results concerning effects on LOS. In a study by Akan et al., [37] 9% of patients with rotavirus positivity were reported to have leukocytes in their stool. In the literature, leukocytes in the stool are detected in up to 30% of subjects with RVGE. In our study, stool leukocytes were observed in 9.3% (n=18) of the children, and a significant relationship with LOS was identified. In addition to major electrolyte disturbances seen in RVGE, our study found that hypokalemia was also a risk factor associated with prolonged LOS. Therefore, prediction and detection of electrolyte disturbances and their management are crucial in RVGE.

It is known that secretory IgA in breast milk protects infants from rotavirus infections[38]. Krawczyk et al., [26] included six meta-analyses in their study and stated that breastfeeding for at least six months is protective against rotavirus infection and reduces the rate of hospitalization. In our study, a negative significant relation was found between breastfeeding duration and the length of stay (LOS) of the children. The LOS of children whose breastfeeding is less than six months was longer than those who breastfed for >6 months. This finding aligns with the literature[38]. In conclusion, breastfeeding for at least six months is important in preventing rotavirus infection and improving the prognosis of the infection.

In a study conducted by Sun et al., [39] it was reported that rotavirus binds to the A blood group antigens through VP8 glycoprotein, and therefore, infection is more common in patients with A blood group. Similarly, Elnady et al., [40] determined that blood group A was highly associated with rotavirus infection. In our study, blood group A was observed in 67.5% (n=131) of the patients with RVGE.

The great majority of children in our study group had blood group A, and thus, comparison of children with respect to blood types may not be reliable; however, our results demonstrated that children with blood group A had longer LOS than children with other blood types. This relationship may be important in assessing the course of the disease in patients with different blood groups, but it is evident that this finding needs to be supported by further studies.

Travel history is an important epidemiological factor for acute gastroenteritis. Patients traveling to areas without implementation of rotavirus vaccine can carry a risk for the disease[41]. With respect to increasing travel habits with small children, it is feasible to suggest that the importance of vaccination against rotavirus is increasing. However, travel history within the prior month before infection was not found to be associated with LOS in our study, demonstrating the need for further studies to evaluate its effect.

Limitations of the Study

The most significant limitation of our study is its retrospective nature. Additionally, reflecting the experience of a single center further limits the generalizability of our findings. We acknowledge that data encompassing a period of 12 months might not be sufficient to create a complete understanding of the clinical characteristics of RVGE; however, the results obtained from our study

can pave the way for conducting subsequent studies on larger cohorts of patients. Further analyses in other areas of Türkiye are needed to validate our findings. Future work should also include data about different rotavirus serotypes to enhance the depth and applicability of the research.

Conclusion

Our results indicate that rotavirus remains a significant and prevalent cause of infectious gastroenteritis among children under five years of age, particularly among those under three years and during the winter season. It manifests with diverse clinical features, including dehydration, electrolyte imbalance, and biochemical disorders. We consider the length of hospital stay (LOS) as one of the markers of the severity of the disease. Factors contributing to the burden of the disease include being younger than 12 months, breastfeeding for less than 6 months, being non-vaccinated, having risky blood group A, the presence of stool leukocytes, and hypokalemia. The findings of this study can serve as valuable background information for the planning and implementation of effective vaccination programs, potentially leading to reduced incidence and severity of rotavirus infections.

Ethics Committee Approval: The study was carried out in compliance with the Helsinki Declaration and was approved by the Ethical Committee of the University of Health Sciences (#167, dated 22.02.18).

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