ROTAVİRUS İNFEKSİYONLARINDA GASTROENTERİT DIŞI BULGULAR

Non-Gastroenteritis Findings In Rotavirus Infections

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ÖZET

Giriş: Rotavirus çocukluk çağında özellikle 5 yaş altı çocuklarda en sık görülen gastroenterit etkenlerinden birisidir. Gastroenterit yakınmalarının yanında viremiye bağlı ekstra-intestinal patolojiler meydana getirmektedir. Bu çalışmada amaç çocuk acil ünitemize rotavirus infeksiyonu ile gelen hastalarda sistemik morbidite ve klinik gidiş üzerine etkilerini ve bunların 2 yıl süreli takibinin değerlendirilmesidir.

Method: 2012-2013 kasım yılları arasında ve 0-18 yaş grubunda 236 hasta çalışmaya alındı. Veriler retrospektif olarak hasta dosya sistemi ve hastane otomasyonundan alındı. Çalışma retrospektif olarak yapılmıştır. İstatistik için ise SPSS 21.0 versiyon programı kullanıldı.

Bulgular: Çalışmaya alınan 236 hastanın sadece 5'inde (%2) ciddi derecede dehidratasyon saptandı. Hastaların çoğunluğunda derecede hafif dehidratasyon mevcuttu. 46 hastada (%23,6) infeksiyon ile ilişkili geçici lenfopeni saptandı. 22 (%9,3) hastada ise geçici nonikterik hepatit tablosu görüldü. 8 hastada (%3,4) febril konvülsiyon ve 1(%0,4) hastada konfüzyon ve 8 (%3,4) hastada ise hipoglisemi mevcuttu. Tüm komorbid durumlar tedavisiz düzeldi ve 2 yıllık takiplerinde kronik ilaç kullanımı veya süregelen hastalık durumu hiçbir hastada görülmedi. Çalışmaya alınan altta yatan bir kronik hastalığı olanlarda yatış süresinin uzadığı ve hipogliseminin daha fazla görüldüğü saptandı.

Sonuç: Rotavirus enfeksiyonu gastroenterit yanında mulitorgan etkilenimi oluşturmaktadır. Çalışmamızda infeksiyon gidişatı sırasında oluşan komorbid durumların benign gidişli, tedavisiz düzelen ve kronik hastalığa yol açmayan durumlar olduğu saptanmıştır.

Anahtar Kelimeler: Rotavirus; Morbidite; Non-ikterik hepatit; Febril konvülsiyon

ABSTRACT

Introduction: Rotavirus is one of the most common gastroenteritis agents especially in children under 5 years of age. In addition to gastroenteritis, rotavirus is associated with extra-intestinal pathologies caused by viremia. We examined systemic morbidities and effects on the clinical courses in pediatric patients admitted to the pediatric emergency unit with rotavirus infection and evaluated these patients over a 2-year follow-up period.

Methods: 236 patients were included in the study admitting to the pediatric emergency unit between November 2012-2013. Patients are 0-18 years old. Study was performed retrospectively. SPSS version 21 software was used for analysis.

Results: The majority of patients had mild dehydration. Forty-six patients (23.6%) had transient lymphocytopenia associated with systemic infection. Temporary non-icteric hepatitis was seen in 22 (9.3%) patients. Moreover, 8 patients (3.4%) had febrile seizures and 1 patient (0.4%) had confusion and 8 (3.4%) patients had hypoglycemia. All comorbid conditions were remedied without treatment and in 2 years follow-up chronic use of medication or ongoing illness was not seen in any patient. Patients with chronic illness were found to have more prolonged length of stay and were found to have more frequent hypoglycemia. It was determined that adenovirus coinfection, dehydration degree and other clinical conditions did not affect the duration of hospital stay and the clinical course.

Conclusion: Rotavirus infection can cause diseases that affect multiple organs. The comorbid conditions that occurred during the course of gastrointestinal infection had a benign course, improved without the need for treatment, and did not result in chronic diseases.

Keywords: Rotavirus, morbidity; Non-icteric hepatitis; Febrile seizures

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INTRODUCTION

Rotavirus is one of the most common causes of gastroenteritis in children, especially in those younger than 5 years old. Rotavirus is responsible for approximately 20% of deaths associated with diarrhea (1). It forms an infection with viremia and can affect organ system as well as intestinal infection (2-3). The most common symptoms are nausea, vomiting, diarrhea fever and extra-intestinal symptoms can occur (4-5). Diarrhea usually lasts one week. However, this can be prolonged in patients with chronic disease or immunodeficiency and can be more severe (6-7). Hepatitis, signs of respiratory infection, myositis, and hemophagocytic syndrome are common extra-

intestinal manifestations (8-9). Moreover, central nervous system complications such as febrile seizures, afebrile seizures, aseptic meningitis, and encephalopathy are also common (10-12).

The aim of this study is to evaluate the non gastroenteritis findings and their effects on clinical symptoms and morbidity admitting to our pediatric emergency department with acute gastroenteritis in rotavirus infection. In addition, we aimed to assess the course of pathologies that developed during the infection period in the 2-year follow-up.

PATIENTS AND METHODS

1. Population

Our study included 236 patients who were admitted to our pediatric emergency department between November 2012 and November 2013 and hospitalized with the diagnosis of rotavirus gastroenteritis. Degree of dehydration was recorded as mild, moderate and severe. Patients that received outpatient treatment for gastroenteritis, antibiotic related gastroenteritis were excluded from the study. Patients who could not tolerate oral feeding, dehydrated at various degrees, and needed parenteral fluid were selected. Our pediatric emergency unit serves an area with a population of approximately 2 million including the rural and urban areas of Kayseri, Turkey.

2. Research and Management

Study was performed retrospectively and was approved by Erciyes University ethics committee. All

records belonging to the patient were taken from the electronic hospital automation system and patient files. Direct microscopy, stool rotavirus and adenovirus antigen testings were performed for all patients. Parasite antigen test was requested from patients who had parasite related medical anamnesis or a family history and stool culture was performed who had bloody diarrhea. Rotavirus can be accompanied by ETEC (Enterotoxigenic Escherichia coli) frequently, but we have not been able to include our study because it has not been studied in our laboratory. Complete blood count and biochemical tests were performed from all patients. C reactive protein was performed in some cases that had initially with unknown fever. Stool cultures included in salmonella, shigella and campylobacter were tested in the bacteriology laboratory, rotavirus and adenovirus antigen testing were performed in the serology laboratory, and other blood tests in were studied in the biochemistry laboratory.

All patients were followed up in single isolation rooms in the pediatric emergency department. Patient examinations and treatment were conducted using isolation and hygiene criteria in order to prevent transmission to other patients. Degree of dehydration of patients were evaluated some certain clinical criters. These criteria are included; mental status, eye, thirsty, skin turgor, capillary refill, urine output, heart rate, mouth and tongue and breathing. All of patients that followed up in emergency rooms who could not be fed because of vomiting. For fluid treatment, we used standard rate of one third mixing glucose and 0.9% serum physiologic. Standard fluid dosage was 2000cc/ m2 and plus deficit to degree of dehydration. After vomiting healed, treatment was completed with ORS (oral rehydration solution). ORS was given at 10 ml/kg every time diarrhea or vomiting.

The data was collected retrospectively. Data was retrieved from the hospital automation system, which includes all data pertaining to patient symptoms at the time of admission, physical examination findings, vital signs, medical interventions, and follow-up course. SPSS version 21 software was used for analysis. Results are expressed as mean \pm SD or median. Shapiro Wilk test was carried out to determine normality of data distribution. Independent sample t test was used for comparison of two independent variables. Chi square test was used to analyze whether there was a relationship between two categorical variables in independent groups. P<0.05 was considered statistically significant, while p > 0.05 was considered not statistically significant.

RESULTS

Our study included 236 patients who presented at our pediatric emergency department between November 2012 and December 2013 with symptoms of gastroenteritis and who were hospitalized due to positive rotavirus antigen results. Among 236 patients, 116 (49.2%) were female and 120 (50.2%) male. The mean age of the patients was 29±34.8 months, median value of the age was 17 months. Incidence of rotavirus infection peaked between the ages of 6-10 months and 16-17 months.

186 (78.8%) patients were mild, 45 (19.1%) patients were moderate and 5 patients had severe dehdyration. The physical examinations of 202 out of 236 patients were normal. Although the majority of patients were admitted with gastroenteritis associated with symptoms, 14 (5.9%) patients had upper respiratory tract infections (URTI) associated with symptoms, 6 (2.5%) patients had lower respiratory tract infections (LRTI) associated with symptoms.

220 (93.2%) out of 236 patients were previously healthy children and did not have any chronic disease. Patients with chronic disease, especially hematologic disease, were found to have a longer duration of hospitalization than other patients. This difference is also statistically significant (p=0.01). The remaining 16 (6.7%) patients had been various chronic diseases, in particular that involving the hematopoietic system (Table 1).

Chronic Disease	Number(n)	Percent(%)
Aplastic anemia	1	0.4
Asthma	1	0.4
Epilepsy	1	0.4
Glycogen storage disease	2	0.8
Hemophagocytic syndrome	1	0.4
Hepatoblastoma	1	0.4
Acute lymphocytic leukemia	1	0.4
Immunodeficiency	1	0.4
Idiopathic thrombocytopenic purpura	1	0.4
Kawasaki	1	0.4
Recurrent pneumonia	4	1.7
Vesicoureteral reflux	4	0.4
No disease	220	93.2
Total	236	100.0

Table 1. Accompanying chronic diseases

The group with chronic illnesses were found to have a longer hospital stay and have a higher incidence of hypoglycemia compared to patients who were previously healthy (p=0.04) (Table 2).

Table 2. Statistical analysis of morbidity in patients

 with chronic disease.

		Chronic Disease Group (n=16)	Previously Healthy Group (n=220)		
Parameter	Unit				
Hospital Stay	Hour	5.2±5.5 *	1.38±0.8		
Severe Dehydration Rate	n	3	2		
Neurological Disorder	n	0	9		
Hepatitis	n	3	31		
Hypoglycemia	n	2**	59		
Lymphocytopenia	n	5	64		
* (p=0.01).					
**(p=0.03)					
n: number of patients					

Patients admitted to our pediatric emergency services were enrolled in the study. The mean length of stay in the hospital was 1.64±1.87 days, while the median length of stay was calculated as 1 day. A total of 177 (75%) patients were discharged after being followedup for 1 day. This suggests that proper hydration or mild dehydration associated with short follow-up period. Five (2.1%) patients with stage 3 dehydration received treatment in the pediatric department. None of the patients developed complications that required intensive care unit.

Laboratory results

In addition to our assessment of dehydration status, biochemical parameters were evaluated in the laboratory. When patients were evaluated for fluid loss and associated renal failure 16 patients (6%) had high BUN (Blood urea nitrogen) values, which are considered pre-renal azotemia.

The blood glucose cut-off limit was set at 45mg/dl (2.5mmol/l) and it was determined that 8 patients (3.4%) had hypoglycemia. In these 8 patients diabetes or another similar disease was not present. Blood glucose levels were normal in all other patients, and hypoglycemia was excluded as a cause in all patients that had seizures. In the complete blood count data; white blood cell count, hemoglobin levels, and platelets were not remarkable values, however 64 patients (27.11%) had lower than normal absolute lymphocyte counts for each age group.

Since rotavirus is capable of causing hepatitis and elevated transaminase levels, we were evaluated both AST levels (Aspartate aminotransferase) and ALT levels (Alanine aminotransferase) separately and in combination. Elevated AST and ALT levels were detected in 22 patients (9.3%). When ALT elevation was evaluated separately, 35 patients (14.8%) were determined to have elevated ALT values. None of these patients exhibited icteric hepatitis symptoms and no patient progressed to Reye syndrome. The elevated transaminase levels resolved in all patients in the post-infection long-term follow-up. None of patients required additional tests or treatment.

Neurological disorders were seizures. In our study,

all patients with febrile seizures were found in the adenovirus negative group. The statistical significance value was calculated as p<0.01. The patients were also classified according to age groups. Three groups were formed according to ages; 0-6 months, 6-24 months and 2 years and above. The reason why we should do grouping in this way; to evaluate the severity, morbidity and course of the disease during the first 6 months of breastfeeding, transition to feeding in infancy period and after infancy. We compared each three groups statistically for severity of disease, morbidity and laboratory values. It was found that the group between 0-6 months applied with a complaint of vomiting and the group above 2 years with diarrhea complaints (p=0.04). In the group above 2 years, more lymphocytopenia was detected statistically than the other two groups (p<0.01). No significant differences were found in terms of other laboratory parameters, clinical severity and morbidity (Table 3).

Table 3. Statistical correlation of morbidity and clinicalfeatures according to age groups.

Parameter	0-6 months	6-24 months	>24 months		
p	(n)	(n)	(n)		
Hepatitis 0.335	3	13	6		
Dehydration 0.381	1	4	0		
Admission complaints 0.04*	7	75	46		
Neurological disorder 0.716	1	6	2		
Adenovirus coinfection 0.053	2	5	10		
Prerenal azotemia 0.49	1	10	9		
Lymphocytopenia 0.01**	3	23	38		
Hypoglycemia 0.747	1	4	4		
Age groups: 0-6 months, 6-24 months, >24months n: number of patients					
* Correlation is significant (p<0.05) in >24 months group					
** Correlation is significant (p<0.05) in >24 months group.					

In our study; in one patient Entamoeba histolytica with direct microscopy as trophozoite form and positive antigen test and and also in one patient Blastocystis hominis parasitology were detected. Blastocystis hominis was not treated because of being in normal flora. Entamoeba histolytica was treated with metronidazole for one week.

When the neurological symptoms were evaluated, we determined that 8 patients (3.4%) were admitted to the emergency due to febrile seizures and 1 patient (0.4%) was admitted due to confusion. In physical examination, no focal focus or neurologic defect was seen in these patients. None of these patients had central nervous system infection, previous seizures, or a history of epilepsy. Electrolyte imbalance and other pathologies were excluded in patients with febrile seizures. Generalized tonic-clonic seizures were observed in all patients with seizures. None of patients shown recurrent seizures during the long-term follow-up and therefore did not require any long-term drug use.

DISCUSSION

In 2015, a study conducted by Prasetyo et al. showed that 12.6% of patients with gastroenteritis develop severe dehydration, and appropriate treatment significantly reduces mortality. In our study only 5 patients (2.1%) had severe dehydration and all of these patients improved with appropriate treatment (13). In our study, severe dehydration was detected very rarely. However, a rate of more than 10% was found in this study in Indonesia. Many factors such as socioeconomic level, accessibility to doctor, nutrition and sanitation can affect this situation. We detected pre-renal azotemia in 16 patients (6%). In all patients renal function returned to normal with proper treatment, and renal pathology and chronic renal failure was not observed at the 2-year follow-up.

A study conducted in 1995 reported that both humoral and cellular immunity are effective in limiting rotavirus infection. This suggests that immunological deterioration in hematological patients increases sensitivity for rotavirus infection (14). In our study no underlying disease was detected in 220 out of 236 patients. Seven of the remaining 12 patients had hemato-immunological pathologies. Patients with chronic illness were found to have a longer stay in the hospital. However, there was no significant difference in other morbidity findings except hypoglycemia.

In our study, clinical examination revealed that in addition to gastroenteritis 14 patients had associated with URTI symptoms and 6 patients had associated with LRTI symptoms. In a study by Fragoso et al. conducted in 1986 that included 30 patients with respiratory tract infections, rotavirus antigen was analyzed in nasal secretions and 2 patients were found to be positive. Despite the limited number of patients, this study may explain the incidence of respiratory infections in patients that presented with gastroenteritis in our study (15). However, since we did not isolate respiratory viruses from nasal swabs from patients, it would be inappropriate to make a definite assessment. Rotavirus causes viremia and systemic symptoms and thus may also lead to hematologic findings. In 2004, by Greenberg et al., a comparison was performed of the hematologic parameters of 101 patients with gastroenteritis with positive or negative rotavirus status, but reported no significant findings (16). In our study, although the total white blood cell count, hemoglobin, and platelet levels were normal, 46 (23.6%) out of 236 patients had a low absolute lymphocyte count compared to the average for the age group. Lymphocytes levels of these patients returned to normal during the follow-up after the infection and no hematological abnormalities were observed during the 2-year follow-up in any patient.

There were different cut-off values in the literature for hypoglycemia. In our study 45 mg/dL was taken (17). In our study, we found that the duration of hospital stay and hypoglycemia were statistically significantly higher in patients with chronic diseases, in particular hematologic diseases (p<0.05). When the literature survey was conducted, it was observed that there was no comprehensive evaluation in this subject except for patients with case-based and immunocompromised patients. In a study published by Pape et al. in 2012, it was reported that there was a healing after bone marrow transplant in a patient's gastrointestinal symptoms having immunodeficiency (18). None of our patients, including that with immunodeficiency receiving chemotherapy in our study, had chronic infections or complications. Only the length of hospital stay was found to be prolonged.

In a 2013 study by Akelma et al. 25 (6.8%) out of 272 patients had isolated ALT elevation, while 69 (25.4%) patients had isolated AST elevation. Similar to our study, temporary hepatitis symptoms were also seen in the study by Akelma et al. (19). One of the systemic effects of rotavirus is temporary non-icteric hepatitis. In another study by Li et al., ALT elevation was detected in 36% of 41 patients (20). However, these studies lacked long-term follow-up data. We did not observed persistent of elevated transaminase levels or persistent elevated liver disease at the 2-year followup. In a study conducted by Smok et al. in 2014, a transient transaminase elevation of 11% was detected (21). In our study, elevated ALT levels were detected in 35 (14.8%) patients and elevated AST levels were detected in 28 (11.9%) patients. The mean elevation of ALT levels was 90 U/L. None of patients with elevated liver function tests developed fulminant hepatitis during follow-up in the emergency service or chronic liver disease at later follow-up.

In a study conducted by Kang et al. between 1999-2011, 17 (2.2%) out of 755 patients had febrile seizures and 42 (5.5%) had afebrile seizures. Despite the low number of patients in our study, the prevalence of febrile seizures was higher than in the study by Kang et al. However, unlike the study by Kang et al., none of the patients in our study had afebrile seizures (22). In a 10-year study by Hung et al. 40 patients (2%) had afebrile seizures and these patients recovered without sequelae and did not receive long-term anticonvulsant treatment (23). In 2010, Lloyd et al., found that febrile seizures in 11 patients and afebrile seizures in 23 patients did not reveal complications or sequelae in long-term follow-up of these patients (24). They evaluated rotavirus-related seizures as relatively benign conditions. In our study, 8 (3.4%) out of 236 patients had febrile seizures. Moreover, similar to these studies, none of the patients that had febrile seizures developed epilepsy or required antiepileptic treatment during the long-term follow-up. The patients that experienced seizures during follow-up did not require long-term drug use and did not develop any ongoing neurological diseases. As a result, similar to these two studies in the literature, we evaluated rotavirus related seizures as benign conditions.

Study Limitations

We could not evaluate the course, morbidity and the severity of the disease in vaccinated patients

CONCLUSION

Rotavirus is responsible for a significant portion of pediatric emergency room admissions. It produces multisystemic effects. In our study, rotavirus was found to cause comorbid conditions such as hepatitis, febrile seizures, hypoglycemia and lymphocytopenia. However, none of these abnormalities were chronic and a rotavirus did not result in pathologies that required long-term treatment. Our vaccination rates were only 2%. We believe that increasing vaccination rates can significantly reduce dehydration related hospitalizations and associated costs.

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