Is Rotavirus Diarrhea a Systemic Viral Infection?

Rotavirus Gastroenteriti Sistemik Viral Bir Enfeksiyon mu?

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Abstract

Objective: To evaluate the development of extraintestinal complications related to rotavirus gastroenteritis, and to determine the impact of systemic rotavirus on disease burden in children with rotavirus-induced diarrhea in our hospital.

Methods: During the two-year study period, 353 children with confirmed rotavirus gastroenteritis were recruited.

Results: Extraintestinal complications occurred in 9.6% (34/353) of all the children. Fourteen patients had central nervous system (CNS) complications related to rotavirus infection. Among these 14 patients, 6 patients had encephalitis; 6 patients, febrile seizures, and 2 patients, aseptic meningitis. Frequency of neutropenia was 2.54% in the study population. Six patients had severe neutropenia [absolute neutrophil count (ANC) <500], and three patients had mild neutropenia [ANC>500]. Ten patients had secondary bacteremia after rotavirus gastroenteritis. Incidence of bacteremia was 2.83%. One patient had myocarditis, which was thought to be associated with rotavirus infection. One death (a child with metabolic disorder) occurred during 2 years.

Conclusion: Our results support the plausibility of rotavirus as an etiologic factor for the clinical manifestations associated with rotavirus infection and highlight the need to pursue studies to determine the involvement of rotavirus as a cause of non-gastrointestinal diseases. The impact of systemic rotavirus on disease burden remains to be determined.

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Key words: Complication, extraintestinal, rotavirus, systemic, viremia

Özet

Amaç: Rotavirüs gastroenteritine bağlı gelişen ekstraintestinal komplikasyonların değerlendirilmesi ve hastanemizdeki rotavirüs nedenli ishal salgınlarında sistemik rotavirüs etkisinin belirlenmesi.

Yöntemler: 2 yıllık çalışma süresi boyunca rotavirüs gastroenteriti olduğu kanıtlanmış 353 çocuk çalışmaya dahil edildi.

Bulgular: Ekstraintestinal komplikasyonlar; çocukların %9.6'sında (34/353) gelişti. Ondört hastada rotavirüs enfeksiyonuna sekonder merkezi sinir sistemi komplikasyonları gözlendi. Bu 14 hastadan 6 hasta ensefalit, 2 hasta aseptik menenjit ve 6 hasta da febril konvülziyon tanısı aldı. Tüm çalışma grubunda nötropeni sıklığı %2.54 idi. Altı hastada ağır nötropeni (mutlak nötrofil sayısı < 500/mm^3 ve 3 hastada hafif nötropeni (mutlak nötrofil sayısı <500mm^3) vardı. On hastada rotavirüs gastroenteriti sonrası sekonder bakteriyemi gelişti. Bakteriyemi insidansı %2.83 olarak değerlendirildi. Bir hastada rotavirüs enfeksiyonuna bağlı olduğu düşünülen myokardit gözlendi. İki yıllık çalışma boyunca sadece bir hasta metabolik bozukluk sonucu hayatını kaybetti.

Sonuç: Çalışmamız, rotavirüsün gastrointestinal sistem dışı hastalıklara da yol açabileceğini ve bu nedenle bu konuda daha fazla çalışma yapılması gerektiğini göstermiştir. Rotavirüs enfeksiyonlarındaki sistemik etkilerin açıklanması için yeni araştırmalar gereklidir.

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Anahtar kelimeler: Komplikasyon, ektraintestinal, rotavirüs, sistemik, viremi

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Introduction

Rotavirus is the main cause of diarrhea-related illness and death in children worldwide. It is associated with more than 2-3 million hospitalizations and up to 600 000 deaths in children aged <5 years; the vast majority occurring in developing countries (1).

The clinical spectrum of rotavirus disease varies from asymptomatic infection to acute, severe, dehydrating diarrhea with vomiting that can be fatal (2). Initially, rotavirus replication was thought to be limited to the gastrointestinal tract in patients with gastroenteritis. This idea has prevailed despite repeated associations of rotavirus infection with systemic symptoms and non-gastroenteric clinical diseases, including respiratory illness and neurological syndromes. Rotavirus RNA and proteins have been detected in the blood of infected children as well as in non-intestinal tissues such as the liver, heart, lung, and central nervous system (3). The role of this antigenemia and viremia in rotavirus disease is puzzling since rotavirus infections have not traditionally been linked to illness outside the gut. Only a few studies have identified extraintestinal manifestations of rotavirus infection, and the credibility of these findings has been questioned because of limited observations (2). Our objectives are to alert physicians to these complications and to infer that damage to gut mucosa occurring during rotavirus gastroenteritis enables rotavirus antigens and RNA to invade the bloodstream, especially in infants.

Two newly developed rotavirus vaccines have shown excellent efficacy and safety profile in clinical trials and are now licensed in Europe (4). Although justification for the use of a vaccine for rotavirus has been based on the occurrence of gastrointestinal and metabolic complications, a third justification would seem to be the occurrence of extraintestinal complications e.g. seizures, secondary bacteremia, and neutropenia.

The aim of this retrospective observational study was to evaluate the development of extraintestinal complications related to rotavirus gastroenteritis and to determine the impact of systemic rotavirus on disease burden in children hospitalized with rotavirus-induced diarrhea admitted to our hospital during a two year period.

Materials and Methods

Study population

The study was performed between July 2007 and July 2009 at the Sisli Etfal Training and Research Hospital for Infectious Diseases in Istanbul, Turkey. During the study period, all the records regarding children aged between 0 and 16 years hospitalized with rotavirus-induced gastroenteritis were anonymously collected. Watery diarrhea (>3 loose stools per 24h) or vomiting that led to >5% dehydration was used as the criteria for hospitalization. A report was compiled for each patient with demographic data and clinical information. The investigation for diagnosis of rotavirus infection was carried out in the Clinical Microbiology Laboratory of the hospital by means of rapid screening tests currently available on the market, such as immunoenzymatic (VIDAS Rotavirus, BioMerieux).

Case definition

In this retrospective study, extra-intestinal complications during the rotavirus infection were ascribed to rotavirus if there were no other (e.g. metabolic disorder, electrolyte imbalance or different infectious agents) factors likely to cause these symptoms. The extra-intestinal complications were defined as follows:

- Seizures: Generalized convulsions with loss of consciousness.
- Encephalitis: Clinical symptoms, usually seizures, decreased consciousness, irritability and mental status change in combination with an abnormal electroencephalogram (EEG) pattern or magnetic resonance imaging (MRI) finding suggesting encephalitis.
- Aseptic meningitis: Clinical symptoms, usually seizures, decreased consciousness, irritability and mental status changes in combination with cerebrospinal fluid (CSF) pleocytosis, absence of signs of parenchymal brain involvement on EEG or cranial MRI.
- Neutropenia: The absolute neutrophil count was calculated by multiplying the total number of white blood cells (WBC) by the percentage of neutrophils and bands. Neutropenia was defined as an absolute neutrophil count (ANC) of less than 1000 cells/mm^3.
- Secondary bacteremia: There was an increase in body temperature (either recrudescence of fever or new-onset fever in previously afebrile infants) several days after admission for rotavirus gastroenteritis. This clinical course, with no apparent source of the fever, prompted us to obtain blood cultures, leading to the diagnoses.

Date of presentation, onset and duration of symptoms and admission were determined for each patient. The presence of symptoms and signs commonly associated with rotavirus gastroenteritis including diarrhea, vomiting, fever, lethargy and dehydration were recorded, as well as a decrease in oral intake and any other symptoms experienced. It was determined whether rotavirus infection was nosocomial (symptoms occurring 3 days after admission for an unrelated illness) or community acquired and whether the child was admitted as an in-patient.

The rotavirus isolated from the CSF sample was positive with the use of a detection primr (primer yoksa primary mi?) pair but could not be genotyped.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16.0 for Windows. Data were expressed as means±Standard Deviation (SD) and ranges.

Results

Clinical and laboratory characteristics

During the two-year study period, 353 children with confirmed rotavirus gastroenteritis were recruited. The ratios of male and female genders were almost equal (53.8% versus 46.2%). In total, 308 (87.3%) patients were community-acquired infection cases, while 43 (12.2%) patients were nosocomially-acquired infection cases. The median age was 15 months (range 1 month to 144 months) in the study group. None of patients had been vaccinated for rotavirus.

The results (mean±SD) of laboratory studies for all the patients were as follows. WBC: 11,500±5317 cells/ mm^3; ANC: 6811±4662 cells/ mm^3; C-reactive protein (CRP): 18.27±37.43 mg/L (normal value<5.0); alanine aminotransferase (ALT): 31.91±24.49 IU/L (normal value < 40); aspartate aminotransferase (AST): 47.87±18.54 IU/L (normal value <40). Of the total,137 patients (38.8%) had an increase in AST alone, while 6 patients (1.7%) had an increase in ALT alone, and fifty-nine patients (17.7%) had an increase in both AST and ALT. The mean AST elevation was 58.7±27.32 IU/L (range, 54 to 136), and the mean ALT elevation was 63.36±32.46 IU/L (range, 44 to 163).

The mean hospitalization time of all the patients was 4.94±2.92 days.

Incidence of complications

In 9.6% (34/353) of all children with rotavirus gastroenteritis, extraintestinal complications occurred and all of these patients had community-acquired rotavirus gastroenteritis.

In this study, 119 (33.7%) patients had mild dehydration; 96 (27.2%) patients, moderate dehydration, and 13 (3.7%) patients, severe dehydration. One hundred sixty-six (47%) patients had isonatremic dehydration; 48 (13.6%) patients, hyponatremic dehydration, and 12 (3.4%) patients, hypernatremic dehydration. One death occurred during the two year period in a child with metabolic disorder. The child developed septicemia with liver and kidney failure and died.

Fourteen patients had CNS complications related to rotavirus infection. Clinical and laboratory characteristics of the patients are shown in Table 1. The incidence of CNS complications was 3.96% in all the patients hospitalized for rotavirus gastroenteritis. Among the 14 patients, 6 patients had encephalitis; 6 patients, febrile seizures, and 2 patients, aseptic meningitis. Serum el ectrolytes were normal in all the children with CNS complications. None of the children suffered any sequelae and chronic seizures after both febrile and afebrile seizures. All of the children with clinical signs of encephalitis and aseptic meningitis were investigated for other bacterial and viral etiologies and the results were negative.

In the study period, of nine patients with neutropenia, 6 had severe neutropenia (ANC<500) and 3 had mild neutropenia (ANC>500); (Table 2). The incidence of neutropenia was 2.54 % in all the study population. The mean number of days of illness, duration of neutropenia, and duration of hospital stay were 3.1±2.3 days, 5.3±3.6 days, and 4.5±3.9 days respectively. The mean WBC was 7140±2800 cells/ mm^3 (range, 3880-9380) and ANC was 559±289 cells/ mm^3 (range, 190-920). None of the children developed sepsis or obvious sequelae of neutropenia.

Ten patients had secondary bacteremia after rotavirus gastroenteritis (Table 3). The incidence of bacteremia was 2.83% in all the patients hospitalized for rotavirus gastroenteritis. All the patients were previously healthy without underlying immunodeficiency or bowel disorder. All of them had either absence of fever or presence of fever with a negative blood culture, negative stool culture, and positive fecal rotavirus antigen assay on admission, and no evidence of phlebitis or other sources of fever, negative urine culture, and positive blood culture for an enteric non-diarrheogenic bacterium when they developed bacteremia.

The myocarditis in one patient was thought to be associated with rotavirus infection. A 9-month-old male infant who had been previously healthy was referred because of vomiting and diarrhea of 2 days duration. The physical examination of the patient was unremarkable except for moderate dehydration. The stool sample was free of blood and mucus, and fecal rotavirus antigen was positive. The blood count, blood chemistry, and venous blood gases were within normal ranges except for mild metabolic acidosis. One day later, he developed tachycardia (180 beats/min) and tachypnea (50 respirations/min) with no fever. The chest radiography was normal. The electrocardiogram showed low voltages and inverted T waves. The rhythm was sinus tachycardia. New laboratory investigations revealed the following laboratory values: WBC: 15,300/mm^3; CRP: 10.9 mg/dl; cardiac troponin I: 0.09 ng/ml (normal range: 0.00-0.06 ng/ml); and creatine kinase (CK-MB): 8 ng/ml (normal range: 0-5). The echocardiogram showed left ventricular dysfunction. The swabs of rectal and nasal mucosa were sent for culture studies to detect any viruses including coxsackie B virus, echovirus, Epstein-Barr virus, cytomegalovirus, and adenovirus. No virus was isolated. The final diagnosis of the patient was established as mild myocarditis caused by rotavirus, and a supportive therapy consisting of a diuretic agent and a low dose of digoxin was initiated. Six days later, his symptoms completely resolved, and he did not develop any complications of myocarditis, such as cardiac rupture, sudden death, and the progression to dilated cardiomyopathy, throughout the hospital stay. The patient appeared to be in excellent health status in the follow-up visit 1 month later.

Table 1. Clinical and laboratory characteristics of cases with CNS complications of rotavirus infection

					PRESENTING SYMPTOMS				LABORATORY STUDIES						
Case	**Age**	**Gender**	**Past medical history**	**Days of Illness**	**Diarrhea**	**Vomiting**	**Fever**	**CNS**	**Electrolytes**	**Rotavirus studies**	**CSF studies**	**CSF radiographs**	**EEG**	**CNS Diagnosis**	**Outcome**
1	16 mo	Male	Healthy	3	Yes	Yes	No	Mental status changes	Normal	Stool antigen positive	Abnormal	CT&MRI normal	Abnormal	Encephalitis	WNL
2	2 yo	Male	Healthy	2	Yes	Yes	Yes	Febrile seizure	Normal	Stool antigen positive	Normal	Not done	Not done	Febrile seizures	WNL
3	10 mo	Female	Healthy	4	Yes	Yes	Yes	Febrile seizure	Normal	Stool antigen positive	Normal	Not done	Not done	Febrile seizures	WNL
4	2 yo	Female	Healthy	2	Yes	Yes	No	Seizures	Normal	Stool antigen positive; CSF Rotavirus PCR positive	Normal	CT normal&MRI abnormal	Abnormal	Encephalitis	WNL
5	13 mo	Female	Healthy	1	Yes	Yes	No	Seizures	Normal	Stool antigen positive; CSF Rotavirus PCR negative	Abnormal	CT normal	Normal	Aseptic meningitis	WNL
6	5.5 mo	Male	Healthy	6	Yes	Yes	No	Irritability	Normal	Stool antigen positive	Abnormal	Not done	Not done	Aseptic meningitis	WNL
7	18 mo	Male	Healthy	1	Yes	No	Yes	Febrile seizure	Normal	Stool antigen positive	Normal	Not done	Not done	Febrile seizures	WNL
8	12 mo	Male	Healthy	3	Yes	Yes	Yes	Decreased consciousness	Normal antigen positive	Stool	Abnormal	CT normal	Abnormal	Encephalitis	WNL
9	13 mo	Female	Healthy	1	Yes	Yes	Yes	Febrile seizure	Normal antigen positive	Stool	Normal	Not done	Normal	Febrile seizures	WNL
10	36 mo	Female	Healthy	Healthy	Yes	Yes	No	Decreased consciousness	Normal	Stool antigen positive; CSF Rotavirus PCR negative	Abnormal	MRI abnormal	Not done	Encephalitis	WNL
11	3 yo	Male	Healthy	1	Yes	Yes	Yes	Mental status changes	Normal	Stool antigen positive	Abnormal	CT&MRI normal	Not done	Encephalitis	WNL
12	9 yo	Male	Healthy	2	Yes	No	No	Seizures	Normal	Stool antigen positive; CSF Rotavirus PCR positive	Normal	CT&MRI normal	Abnormal	Encephalitis	WNL
13	18 mo	Female	Healthy	2	Yes	Yes	Yes	Febrile seizure	Normal	Stool antigen positive	Normal	Not done	Not done	Febrile seizures	WNL
14	16 mo	Male	Healthy	2	Yes	No	Yes	Febrile seizure	Normal	Stool antigen positive	Normal	CT normal	Not done	Febrile seizures	WNL

*WNL indicates within normal limits

Table 2. Clinical and laboratory characteristics of cases with neutropenia complications of rotavirus infection

					LABORATORY STUDIESOMS						
Case	**Age**	**Gender**	**Past medical history**	**Days of Illness**	**WBCX 1000_L**	**ANCX 1000 _L**	**Hemoglobin, mg/dL**	**Plateletsx 1000/_L**	**Duration of neutropenia, days**	**Duration of hospital stay, days**	**Outcome**
1	9 mo	Male	Recurrent urine tract infection	6	5.51	0.620	10.3	177	6	3	Healthy
2	18 mo	Male	Healthy	3	7.31	0.900	11.8	326	4	4	Healthy
3	18 mo	Male	Healthy	1	9.38	0.498	11.2	481	7	4	Healthy
4	3 mo	Female	Healthy	2	7.14	0.680	12.6	385	5	5	Healthy
5	7 mo	Female	Healthy	3	4.30	0.450	12.2	217	7	4	Healthy
6	7 mo	Female	Healthy	2	7.25	0.92	11.6	364	4	6	Healthy
7	1.5 mo	Male	Healthy	3	7.98	019	9.7	646	5	3	Healthy
8	30 mo	Female	Healthy	2	3.88	0.37	12.3	270	4	5	Healthy
9	6.5 mo	Female	Healthy	6	4.50	0.39	10,2	349	6	7	Healthy

Discussion

Rotavirus is one of the most common causes of gastroenteritis among children, causing significant morbidity. Since initial identification of rotavirus in children with diarrhea approximately 35 years ago, rotavirus tropism has been thought to be limited to small intestinal epithelial cells, and therefore, confined to the intestine. Studies examining rotavirus infection and disease in experimental animal models clearly demonstrate infectious rotavirus at systemic sites. All available data suggest that, viremia is part of the natural course of rotavirus infection, the rotavirus is not confined to the intestinal tract, and the rotavirus routinely disseminates beyond the intestine to systemic sites (3). The demonstration by Morrison et al (5) of rotavirus RNA in the heart and central nervous system of 2 deceased children, was supported by 2 Japanese groups (6,7) who documented rotavirus RNA in serum by reverse-transcription (RT) polymerase chain reaction (PCR). Blutt et al recently demonstrated rotavirus antigenemia and viremia by RT-PCR in 3 of 6 immunocompetent children with documented RV diarrhea (8). In our study, the incidence of extraintestinal complications related to rotavirus gastroenteritis was 9.6% (34/353).

Rotavirus gastroenteritis is known to be accompanied by some neurological manifestations, such as acute encephalitis/encephalopathy or seizures; however, the pathophysiology is not yet fully understood. One plausible explanation by which rotavirus could affect CNS is rotavirus direct invasion. Rotavirus RNA or antigen could be detected in rotavirus gastroenteritis patients' blood or CSF, with or without any neurological manifestations (9). Moreover, extraintestinal rotavirus replication was detected in mice (10). These results are compatible with rotavirus direct CNS invasion. However, rotavirus antigen and/or PCR were not always positive in encephalitis/encephalopathy associated with rotavirus gastroenteritis; rotavirus was detected in 5 out of 8 children and no rotavirus antigen was detected in CSF, while rotavirus PCR was positive in only 3 out of 8 cases (11).

Neurological manifestations occur in approximately 2-5% of patents with rotavirus gastroenteritis (11). CNS complication was the most common extra-intestinal complication, and present in 3.91% of all the children in our study. Afebrile benign convulsions associated with gastroenteritis were first described in 1982 (12). Since then, several case reports have appeared in the literature, most of which showed an association of afebrile seizures with the presentation of gastroenteritis (13-16). In our study, 3 of 14 patients with CNS complications of rotavirus infection presented with afebrile seizures, and their diagnoses were made as encephalitis based on their clinical and laboratory values. Rotavirus gastroenteritis may be associated with high fever and consequently, typical febrile seizures may occur. On the other hand, there are several reports of febrile seizures associated with rotavirus gastroenteritis (17,18). Pang et al found RT-PCR rotavirus in the CSF on the day of onset of fever in rotavirus gastroenteritis (17). They suggested extraintestinal spread of rotavirus at an early phase of rotavirus infection with systemic symptoms, including high fever and febrile convulsions. Similarly, in our study, 6 patients were diagnosed with febrile seizures related to rotavirus infection because the results of all the studies on infection focus were negative except for rotavirus gastroenteritis. The results of CSF studies in the patients with febrile seizures associated with rotavirus infection were normal. Whether rotavirus was directly involved in the induction of convulsions or whether the seizures were induced by high fever cannot be concluded. However, as the course of disease was benign, it would seem possible that systemic spread of rotavirus may take place in the absence of encephalitis. In children with rotavirus gastroenteritis, CNS disease may be present and should be considered when CNS symptoms are present. An appropriate evaluation includes a lumbar puncture with routine studies and a CSF RT-PCR for rotavirus should be performed.

Published data on the association of neutropenia with infectious diarrhea in children are limited (19,20). Greenberg et al found that mild neutropenia (ANC>500) occurs in about 10% of children hospitalized for rotavirus-induced gastroenteritis (19). In their study, none of the children developed sepsis or obvious sequelae of neutropenia, as in our study. Our results differ from those of Greenberg et al. and suggest that severe (ANC<500; 6/9, 66.6%) and mild (ANC>500; 3/9, 33.3%) neutropenia occurred in about 2.54% of the children hospitalized for rotavirus-induced gastroenteritis. It is possible that the differences between these studies result from differences in patient populations. We studied a population with almost an equal gender distribution in ethnically homogeneous Turkey. In contrast, the population in the study by Greenberg et al was predominantly male and reflected the ethnic heterogeneity of urban Memphis. We suggest that severe or mild neutropenia seen in the context of rotavirus-induced diarrhea does not require further evaluation unless it persists or is associated with other factors, such as sepsis.

Even though enteric Gram-negative rod (EGNR) bacteremia has been described as a possible complication of gastroenteritis (21), very few reports of EGNR bacteremia as a complication of rotavirus-associated acute diarrhea have been published to date (22,23). We describe 10 patients with confirmed rotavirus gastroenteritis complicated by secondary bacteremia (Table 3). The hallmark of these events was an increase in body temperature (either recrudescence of fever or new-onset fever in previously afebrile patients) several days after admission for rotavirus gastroenteritis. This clinical course, with no apparent source of the fever, prompted us to obtain blood cultures, leading to the diagnoses. This clinical course is typical of secondary bacterial complications of other viral infections such as varicella or viral respiratory infections. Although this complication is apparently rare, the lack of descriptions is probably also related to lack of awareness of this complication and failure to obtain blood cultures later in the course of rotavirus gastroenteritis. *E.cloacae* and *K.pneumonia*, members of the *Enterobacteriaceae* family, are normal commensals of the human intestine. These facultative anaerobes are distributed ubiquitously throughout most of the gut, including the small intestine, as opposed to obligatory anaerobes, which are usually confined to the colon. It is therefore conceivable that the mucosal damage during rotavirus infection may be sufficient to allow bacterial translocation, leading to secondary bacterial translocation, which results in secondary bacteremia, notably in the relatively vulnerable intestinal wall of young infants (24). This was supported by the findings of our study, because most of the patients with secondary bacteremia after rotavirus gastroenteritis were young infants. Thus, when a second peak of fever with no obvious source occurs in infants with rotavirus gastroenteritis, blood cultures should be obtained, and empiric antibiotic therapy should be considered pending the culture results.

The causes of myocarditis are diverse and infectious etiologies, particularly viral, and most common in children. The most common causes of viral myocarditis are enterovirus and adenovirus. Affected children can present with a broad clinical spectrum of disease that can be acute, fulminate, or chronic. In recent years, several reports supported that rotavirus also caused myocardial tissue damage that led to myocarditis in animals and humans (5,25-27). Yao et al. investigated the extraintestinal dissemination of rotavirus in immunodeficient mice. In their study, small intestinal villi, gastric lamina propria and cardiac myocytes exhibited pathological changes in the mice with oral rotavirus administration (27). Morrison et al. reported 2 cases of fatal rotaviral infection in a 1-year-old and 4-year-old (5). In each case, the illness showed a rapid systemic course dominated by cardiac and central nervous system involvement.

Table 3. Clinical and laboratory characteristics of cases of secondary bacteremia after rotavirus gastroenteritis

Case	Age	Gender	At Admission				Day of Recrudescence of Fever Or New-Onset Fever	*At occurrence of Bacteremia*				
			Fever, ºC	Blood Culture	CRP (mg/L)	Leukocyte Count, Cells per mm³ (Neutrophils)		Fever, ºC	Blood Culture	Urine Culture	CRP (mg/L)	*Leukocyte Count, Cells per mm³ (Neutrophils)*
1	12 mo	Male	38,0	Negative	7.1	11,050 (5960)	4	40.0	*E. coli*	Negative	38.4	19,000 (16,700)
2	12 mo	Female	36,2	Not done	0.1	10,430 (6420)	3	39.5	ESBL (+)*E. coli*	Negative	60	17.940 (9590)
3	9 mo	Male	36,5	Not done	4.3	13,560 (8650)	4	39.3	*E. cloacae*	Negative	139,6	27,430 (16 940)
4	15 mo	Female	36,0	Not done	3.4	6570 (2570)	3	38,7	*E. cloacae*	Negative	53,2	8630 (5930)
5	11 mo	Male	37,0	Negative	0.1	8750 (3280)	5	39	ESBL (+)K. oxytoca	Negative	134	16430 (11750)
6	4 yo	Male	38,2	Negative	12	11,600 (5600)	5	40	ESBL (+)*E. coli*	Negative	58,3	43,890 (35,500)
7	12 mo	Female	39,4	Negative	0,1	11,930 (7980)	4	40,2	*K. oxytoca*	Negative	133,8	16,500 (8660)
8	60 mo	Female	36,2	Not done	0.7	10,990 (8670)	4	38.8	*K. pneumoniae*	Negative	139	26,000 (21,800)
9	9 mo	Male	36,7	Not done	0.1	6990 (5040)	4	38,9	ESBL (+)*E. coli*	Negative	147	13,830 (8440)
10	24 mo	Female	37	Negative	0.5	10,730 (7870)	3	39.3	*E. coli*	Negative	131	25,860 (20,800)

Cioc et al. also reported four cases of fatal rotavirus myocarditis (25). In our study, we presented one child with myocarditis which was thought to be related to rotavirus infection. Endomyocardial biopsy (EMB) is the gold standard for the diagnosis of myocarditis. The American Heart Association recommends that EMB in children is reasonable in the setting of unexplained cardiomyopathy. Indications include fulminate or acute unexplained heart failure, cardiac transplant rejection monitoring, certain unexplained arrhythmias, and idiopathic dilated cardiomyopathy (26). Our patient's myocarditis was not fulminate, and the patient had no symptoms to match the criteria that would require an EMB. We conducted studies for most common viral etiologic agents that cause myocarditis, and the results were negative. Considering the occurrence of rotavirus gastroenteritis and the lack of evidence of other causes, the patient's final diagnosis was established as mild myocarditis caused by rotavirus.

Rotavirus can also cause slight elevation of the liver transaminases. The ability of the virus to result in abnormalities in hepatic transaminases, alkaline phoshatase, or bilirubin has rarely been reported (28,29). Recently, Zanelli et al documented a true case of hepatitis associated with rotavirus infection (30). In addition, Teitelbaum et al. demonstrated in their study that 15/75 (20%) children with rotavirus gastroenteritis had associated elevation of their liver transaminases (28). Our results were similar to the results of the study by Teitelbaum et al in that 59/353 (17.7%) children had elevated ALT and AST during their rotavirus gastroenteritis in our study. Physicians should thus be aware of this association and its relative frequency, and rotavirus should be added to the long list of hepatotrophic viruses.

Two rotavirus vaccines were recently licensed in Turkey. Knowledge of the local burden of disease is needed for decision makers and health professionals to consider rotavirus vaccination policies. Although justification for the use of a vaccine for rotavirus has been based on the occurrence of gastrointestinal and metabolic complications, a third justification would seem to be the occurrence of extraintestinal complications. The overall incidence of this association remains unclear. However, the combined cost and stress of hospitalization, diagnostic testing, prompting prolonged medical therapy, appears to justify attempts at prevention.

Solid evidence now exists in children and animals that rotavirus infections routinely extend beyond the intestine to the blood and have the potential to be widely distributed and cause nonintestinal disease. Questions of foremost importance to clinicians are whether systemic infection results in disease, identification of this disease(s), and how systemic infections might affect the clinical management of rotavirus cases and contribute to the healthcare burden for rotavirus infections. Pediatricians should be alert to rare but potentially serious extraintestinal complications of rotavirus gastroenteritis. Additional clinical studies, basic research in animal and in-vitro models will be critical to the full assessment of the true spectrum and burden of extraintestinal rotavirus disease in children, and to determine whether a national rotavirus immunization program prevents cases of extraintestinal rotavirus disease. Furthermore, the information gained in these studies will help direct and enlighten the clinical perspective of rotavirus as a systemic infection.

Conflict of Interest

No conflict of interest is declared by the authors.

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