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# Systemic Manifestation of Rotavirus Infection in Children: A Report of Three Cases

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## Abstract

**Introduction:** Rotavirus is a leading cause of acute gastroenteritis in children. Although the clinical complaints associated with rotavirus are generally gastrointestinal, including vomiting and diarrhea, data suggest that it can also cause symptoms that extend beyond the gastrointestinal tract.
**Case Presentations:** We report three pediatric cases of rotavirus infection: one accompanied by encephalopathy and two with elevated hepatic transaminase activity. The patients were admitted to Dr. Sami Ulus maternity and children's health and diseases training and research hospital, Ankara, Turkey, from 2012 - 2014. The presented patients' aspartate aminotransferase (AST) (1765-2614 IU $L^{-1}$) and alanine aminotransferase (ALT) (1448-3558 IU $L^{-1}$) levels are, to date, the highest reported levels associated with rotavirus infections, and suggest that the rotavirus can cause severe hepatic transaminase elevation.
**Conclusions:** This report aimed to increase awareness of the occurrence of extra-intestinal systemic manifestations of rotavirus infection. Although such cases may be rare, they still suggest that that rotavirus is a systemic viral infection.

*Keywords:* Rotavirus Infection, Systemic Manifestation, Children, Infant

## 1. Introduction

Rotavirus is a non-enveloped double-stranded RNA virus that causes severe gastroenteritis in > 90% of children under three years of age (1). Since rotavirus infection was first identified in children with diarrhea, rotavirus tropism has been thought to be limited to the small intestinal epithelial cells and therefore confined to the intestine; however, it has been shown that viremia occurs in children during the course of acute rotavirus infection, and a few reports of non-gastrointestinal-associated manifestations, including central nervous system involvement and elevated hepatic transaminase activity, have been reported (1-3). Herein, we report three pediatric cases of rotavirus gastroenteritis, two of which were accompanied by severe elevation in hepatic transaminase activity (of which one had the highest level of activity every published in the English-language literature) and one that was diagnosed as encephalopathy. This report aims to increase awareness of extra-intestinal systemic manifestations of rotavirus infection.

## 2. Case Presentations

### *2.1. Case One*

A female seven months of age presented to our hospital (Dr. Sami Ulus Maternity and children's health and diseases training and research hospital, Ankara, Turkey) with fever, vomiting, diarrhea, and feeding intolerance in March of 2013. Her medical history and family history were unremarkable. The patient's history of medication use and toxin exposure was negative. Physical examination showed mild dehydration. Laboratory findings revealed elevated aspartate aminotransferase (AST) (1765 IU $L^{-1}$; normal range: 0 - 48 IU $L^{-1}$) and alanine aminotransferase (ALT) (1448 IU $L^{-1}$; normal range: 0 - 39 IU $L^{-1}$), and normal gamma glutamyltransferase (GGT) (14 IU $L^{-1}$; normal range: 0 - 40 IU $L^{-1}$), serum total bilirubin (0.3 mg $dL^{-1}$; normal range: 0 - 2 mg dL-1), serum conjugated bilirubin (0.2 mg $dL^{-1}$; normal range: 0 - 0.5 mg $dL^{-1}$), and alkaline phosphatase (ALP) (193 IU $L^{-1}$; normal range: 0 - 500 IU $L^{-1}$) (measured by Architect C 16,000). Her acute phase reactants, serum electrolytes, coagulation parameters, serum glucose and albumin levels, and renal function test results were normal.

Abdominal ultrasonography showed hepatic parenchymal hyperechogenicity without hepatomegaly.

Viral markers (hepatitis A [HAV], hepatitis B [HBV], hepatitis C [HCV], Epstein-Barr virus [EBV], cytomegalovirus [CMV], adenovirus, and herpes virus) were all negative. Stool antigen testing was positive for only rotavirus; no other pathogens were cultured from the stool or blood. Metabolic screenings were all normal. The patient was hospitalized and administered intravenous hydration. During follow-up, her ALT level reached a maximum of 2571 IU $L^{-1}$ and the AST level decreased slightly. Symptoms of gastroenteritis completely resolved on day eight of hospitalization, as the hepatic transaminase levels dropped (AST: 41 IU $L^{-1}$ and ALT: 203 IU $L^{-1}$). On day 12 of the follow-up, the patient's AST and ALT levels returned to normal (AST: 40 IU $L^{-1}$ and ALT: 40 IU $L^{-1}$).

### 2.2. Case Two

A 2.5-year-old male who was being monitored for autism spectrum disorder presented to our hospital (Dr. Sami Ulus maternity and children's health and diseases training and research hospital, Ankara, Turkey) with three days history of fever, vomiting, and diarrhea in November of 2014. His medical history and family history were unremarkable. Physical examination showed fatigue and lack of appetite. Laboratory findings revealed high AST and ALT levels (2614 IU $L^{-1}$ and 3558 IU $L^{-1}$, respectively), and normal GGT (33 IU $L^{-1}$), serum total bilirubin (0.5 mg $dL^{-1}$), serum conjugated bilirubin (0.2 mg $dL^{-1}$), and ALP (153 IU $L^{-1}$) levels (measured by Architect C 16,000). Acute phase reactants, renal functions, serum electrolytes, serum glucose, and albumin were normal, as were the coagulation parameters.

Abdominal ultrasonography showed hepatic parenchymal hyperechogenicity without hepatomegaly. The serology results for HAV, HBV, HCV, EBV, CMV, adenovirus, and herpes virus were negative. The patient's autoimmune hepatitis autoantibodies were negative, and alpha-1 antitrypsin and ceruloplasmin levels were normal. Stool antigen testing was positive only for rotavirus; again, in this case, no other pathogens were cultured from the stool or blood. Metabolic screening investigations were normal. The patient was hospitalized for close follow-up. The patient's ALT and AST levels decreased slightly after hospitalization, decreased by 50% on day five of hospitalization, and were normal on day 14 (AST: 40 IU $L^{-1}$ and ALT: 46 IU $L^{-1}$), after which he was discharged. At one month post presentation, the patient's AST level was 28 IU $L^{-1}$ and the ALT level was 16 IU $L^{-1}$.

### 2.3. Case Three

A two-month-old male presented to our hospital (Dr. Sami Ulus maternity and children's health and diseases training and research hospital, Ankara, Turkey) due to fever, diarrhea (eight episodes/day), vomiting, and eye convulsion and deviation in December of 2014. His medical history and family history, including the pregnancy, were unremarkable. Physical examination showed that he was drowsy, mildly dehydrated, and lethargic. Cerebrospinal fluid (CSF) was obtained for analysis via a lumbar puncture and the findings were normal as follows: glucose levels were 65 mg $dL^{-1}$, and protein levels were 44.9 mg $dL^{-1}$. The serum glucose level was 90 mg $dL^{-1}$ and the CSF culture was negative. Laboratory findings for acute reactants, renal functions, electrolytes, and liver functions were normal. The cranial ultrasound examination and electroencephalography were also normal.

In this case as well, stool antigen testing was positive only for rotavirus, and no other pathogens were cultured from the stool or blood. The patient was hospitalized for intravenous hydration, empiric antibiotic treatment, and follow-up. Diarrhea resolved on day five of hospitalization and encephalopathy resolved without any reoccurrence on day 10. Neurological examination was normal. The patient exhibited age-appropriate motor and developmental skills on day six of hospitalization and was scheduled for post discharge follow-up (Table 1).

## 3. Discussion

Worldwide, rotavirus is the primary cause of gastroenteritis in children under the age of five years and causes approximately 114 million episodes of childhood gastroenteritis annually (4). Rotavirus-induced diarrhea and vomiting can cause severe dehydration and lead to childhood mortality in developing countries. Additionally, rotavirus gastroenteritis severely strains the healthcare budgets of developed countries (5). Rotavirus frequently involves the epithelial surface of the small intestine and usually presents with local infection of the gastrointestinal system (3).

All currently available data suggest that viremia is a part of the natural course of rotavirus infection, that rotavirus is not confined to the intestinal tract, and that it routinely disseminates systemically beyond the intestine (6). Such systemic manifestations as elevated hepatic transaminase, in addition to the features of rotavirus gastroenteritis, have also been reported. The incidence of elevated ALT and AST is reported to be 11.5% - 72% and 21% - 88.5%, respectively (3, 7, 8). Rotavirus affects the liver in 15.4% of cases with gastroenteritis (7). The mean AST and ALT levels vary by study, but are usually mildly to moderately elevated (< 150 IU $L^{-1}$), which is referred to as mild rotavirus-associated hepatitis (7-9).

To the best of our knowledge only one patient with an AST level of 448 IU $L^{-1}$ and ALT level of 225 IU $L^{-1}$ was reported

**Table 1.** Description of Cases on Admission

| Variables | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| **Age** | Seven months old | 2.5 years old | Two months old |
| **Gender** | Female | Male | Male |
| **Clinical characteristics** | Elevated liver enzymes | Elevated liver enzymes | Encephalopathy |
| **Liver enzyme levels** | | | |
| Aspartate aminotransferase (AST), IU $L^{-1}$ | 1765 | 2614 | - |
| Alanine aminotransferase (ALT), IU $L^{-1}$ | 1448 | 3558 | - |

as having rotavirus-associated hepatic transaminase elevation (9). The presented patients' AST (1765-2614 IU $L^{-1}$) and ALT (1448-3558 IU $L^{-1}$) levels are, to date, the highest reported levels associated with rotavirus infections, and suggest that rotavirus can cause severe hepatic transaminase elevation. No other case series or case report has revealed other clinical or laboratory signs of hepatic insufficiency, such as hypoalbuminemia, hypoglycemia, or low coagulation parameters (7-9). The presented patients did not have any symptoms or signs of hepatic insufficiency either. Normalization of hepatic transaminase levels was reported to occur within 9 - 15 days of onset of the disease (7, 9). Although the presented patients had the highest hepatic transaminase levels reported to date, they returned to normal on day 12 - 14 of follow-up. Based on the present findings, we believe that physicians should be aware of the important extra-intestinal manifestations of rotavirus infection and their relatively high frequency in children, and perhaps rotavirus should be considered as a hepatotropic virus. Furthermore, rotavirus infection should be a consideration when evaluating the etiology of hepatic transaminase elevation in patients with acute gastroenteritis.

Rotavirus gastroenteritis is reported to be accompanied by some neurological manifestations, such as acute encephalitis/encephalopathy or seizures (1, 10-13). The pathophysiology of nervous system involvement is not yet fully understood, but might be associated with direct invasion of the central nervous system by rotavirus; thus, the rotavirus RNA or antigen could be detected in rotavirus gastroenteritis patients' blood or CSF in the absence or presence of neurological symptoms (13). Nonetheless, PCR of CSF of all patients who have neurological manifestations did not completely correlate, so the direct invasion of the virus is not yet completely established in such cases (10). Another possible mechanism of extra-intestinal rotavirus manifestation could be secondary involvement of the central nervous system during acute viral infection. Rotavirus directly destroys enterocytes via the effect of nonstructural protein-4 (NSP-4). NSP-4 alone induces nitric oxide (NO) metabolites in association with rotavirus infection. It was reported that NO metabolites are elevated in both serum and CSF in cases of rotavirus infection, indicating the neurotoxic effect in patients with neurological manifestations and rotavirus gastroenteritis (14). Cranial MRI in patients with rotavirus infection commonly shows pathological signals in the cerebellum and posterior brain, and reversible hyperintensity in the splenium of the corpus callosum (15, 16). These mild, reversible changes are known as mild encephalitis/encephalopathy with a reversible splenic lesion (16). Neurological manifestations occur in 2% - 5% of patients with rotavirus infection (11). Rotavirus gastroenteritis can be associated with high fever and, consequently, typical febrile seizures can occur, and there are several reports of febrile seizures associated with rotavirus gastroenteritis (12, 13). For instance, our third case had a clinical course of febrile seizure at presentation, but encephalopathy persisted for five days, suggesting the concordance of clinical entities. Cranial MRI was not performed on this patient, as the parents declined to give consent.

In conclusion, the presented cases add to a significant body of data from other studies on children and animals that indicate rotavirus infection can occur beyond the intestine, with the potential to be widely distributed and cause extra-intestinal symptoms. Therefore, pediatricians should be aware of the rare but potentially serious extra-intestinal manifestations of rotavirus infection.

## Footnote

**Authors' Contribution:** All authors followed and treated the patients, and collaboratively wrote the manuscript.

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