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# Rotavirus-associated intussusception followed by spontaneous resolution

## Rotavirus enfeksiyonu ile birlikte gelişen intussusepsiyonu takiben kendiliğinden iyileşme

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*Rotavirus was related to causing intussusception when the first generation rotavirus vaccine was introduced. However, the association between natural rotavirus infection and intussusception remains an area of concern and controversy. A few studies have found that rotavirus infection can cause intussusception. On the other hand, several studies were unable to find an association of intussusception with natural rotavirus infection. Herein, we describe a patient who developed intussusception following rotavirus diarrhea during the course of hospitalization and recovered by spontaneous resolution the next day. This rotavirus belonged to serotype G9P[6]. The case is presented here as an evidence that natural rotavirus infection is associated with intussusception. Comprehensive research is needed to identify whether intussusception by rotavirus has a propensity to resolve spontaneousey.*

**Key words**: Rotavirus, intussusception, child.

*İlk kuşak Rotavirus aşısı kullanıma girdiğinde, rotavirusun intussusepsiyona neden olduğu bildirilmiştir. Bununla birlikte doğal rotavirus infeksiyonu ve intussusepsiyon ilişkisi ilgi ve tartışma gerektiren bir konudur. Rotavirusun intussusepsiyona neden olduğuna dair birkaç çalışma vardır. Diğer taraftan çoğu çalışmada da doğal rotavirus infeksiyonu ile intussusepsiyon arasında bir ilişki tespit edilememiştir. Bu çalışmada rotavirus diaresini takiben hastanede yatış sürecinde intussusepsiyon gelişen ve takip eden günde spontan redüksiyon ile düzelen bir hasta sunuyoruz. Bu rotavirus serotip G9P idi. Bu vaka doğal rotavirus infeksiyonunun intussusepsiyonla ilişkili olabileceğini kanıtlamak için sunulmuştur. Rotavirusun neden olduğu intussusepsiyonun spontan redüksiyonla çözümlenmeye eğilimli olup olmadığına dair kapsamlı araştırmalara ihtiyaç vardır.*

**Anahtar kelimeler**: Rotavirus, intussusepsiyon, çocuk

## INTRODUCTION

Intussusception is one of the most common causes of acute abdomen in children between 6 months and 2 years of age (1). It is idiopathic in almost all cases. A recognizable anatomic lesion acting as a lead point is found in only 2–12% of all pediatric cases (2). Several reports have indicated that microorganisms might be involved in the pathogenesis of intussusception in a number of cases. Bacteria isolated from cases of intussusception include *Yersinia enterocolitica* and *Y. pseudotuberculosis, Clostridium difficile, Mycobacterium avium, Aeromonas* spp., *Salmonella enterica* serovar *Typhimurium, Escherichia coli, Shigella* spp., and *Pasteurella pseudotuberculosis* (3). Viral pathogens, mostly adenovirus, enterovirus, human herpesvirus and Epstein-Barr virus, are reported in 20–50% of the childhood intussusception cases (4). Rotavirus was implicated as a cause of intussusceptions when the first generation rotavirus vaccine Rotashield (Wyeth Laboratories, Inc.; Marietta, Pennsylvania, USA), a rhesus-human reassortant tetravalent vaccine, was introduced (5). During the late 1970s and early 1980s, three studies from Japan, France and Australia found the association

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of rotavirus in triggering intussusception (6-8). A comprehensive review in 1998 concluded that those studies constituted insufficient evidence to conclude that rotavirus infection caused intussusception (9). Other studies were also unable to find an association between intussusception and natural rotavirus infection (4,10-12). However, study in an animal model lends experimental support for the role of rotavirus in the development of acute intussusception (3). Here, we present an 18-month-old boy with natural rotavirus diarrhea who developed intussusception during hospitalization that spontaneously resolved.

## CASE REPORT

An 18-month-old boy admitted to Ankara Training and Education Hospital with a history of vomiting and fever for the last 2–3 days. Fifteen days before, the patient presented to a physician with the same complaints and was treated with antibiotics and antipyretics. On admission, his body temperature was 36°C and body weight was 13 kg. To rule out meningitis, a lumbar puncture was done. The cerebrospinal fluid (CSF) was clear on appearance and the pressure was within normal limits. The results of laboratory investigation of CSF were as follows: no erythrocyte was observed, total leukocyte count was 270/mm$^3$, consisting of 30% polymorphonuclear neutrophils and 70% mononuclear leukocytes, and protein concentration was 569 mg/L (reference: 150–450 mg/L) and glucose 55 mg/L (reference: 60–80 mg/L). CSF culture did not show growth of any microorganisms. A treatment was stared with ceftriaxone, paracetamol and dexamethasone.

On the day of admission, the patient developed diarrhea with frequency of 5–6 times/day. There was no blood in the stool. No erythrocytes, leukocytes, protozoal cyst, trophozoite or parasite eggs were found in the stool by microscopic examination. Stool culture did not show growth of pathogenic bacteria. Enzyme immunoassay (Dipstick 'Eiken' Adeno, Eiken Chemical Co. Ltd.; Tokyo, Japan) of stool was negative for adenovirus. Enzyme linked immunosorbent assay (Rotaclone, Meridian Bioscience Inc.; Cincinnati, OH, USA) of the stool was positive for group A rotavirus. The G and P serotypes of rotavirus were determined as follows: the genomic dsRNA was extracted from the stool utilizing the phenol-chloroform-isoamyl alcohol method (13). The VP7 gene was amplified with consensus primers Beg9 and End9 (14). The nucleotide sequence of the VP7 gene was determined by BigDye terminator v3.1 cycle sequencing kit (Applied Biosystems; Foster City, CA, USA) according to the manufacturer's instruction, and the product was run in ABI Prism 3100 Genetic Analyzer (Applied Biosystems). Serotype was established by sequence identity search with BLAST. The VP4 gene was amplified with consensus primers con-2 and con-3 (15), and the P type was identified with genotype-specific primers for P[8], P[4], P[6] and P[9], as described previously with a few modifications as follows (16). For VP7 and VP4 gene amplification, reverse transcription polymerase chain reaction (RT-PCR) was done with AccessQuick RT-PCR (Promega Corporation; Madison, WI, USA). For P-specific genotyping, PCR Master Mix (Promega) was used.

Initial laboratory examination revealed a total red blood cell count of 4.88x10$^6$/μl (reference: 3.8–4.8x106/μl). Hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin were 9.29 g/dl (reference: 11–14 g/dl), 58.6 fL (reference: 70–84 fL) and 19 pg/erythrocytes (reference: 22–30 pg/erythrocytes), respectively, indicating a slightly anemic child; the erythrocyte sedimentation rate was 31 mm/1$^{st}$ hour (reference: 0–10 mm/1$^{st}$ hour). Serum C-reactive protein, glucose, urea, creatinine, uric acid, total bilirubin, alanine transaminase and aspartate transaminase were within the normal ranges. As for serum electrolyte levels, sodium, potassium, chloride, calcium, and magnesium were all within normal ranges.

On the third day of admission, the patient developed abdominal pain and did not pass stool. Examination revealed findings of acute abdominal distension, and no bowel sound was heard. Plain abdominal radiograph showed dilated bowel loops and multiple air-fluid levels (Figure 1a). The ultrasonogram of the abdomen showed 'target sign' confirming intussusception (Figure 1b). According to the Brighton Collaboration Working Group guidelines, our case fell in Level 1 of diagnostic certainty (17). Intravenous fluid was started and the patient was kept under observation. Within eight hours, there was no abdominal pain and the abdominal distension had started to decrease. Therefore, no intervention was done and the patient remained under further observation. On the fourth day, there was no distension, and the bowel sound normalized. A lumbar puncture was done and clear CSF was obtained. The laboratory results of CSF was as follows: no erythrocytes, leukocyte co-

unt 10/mm$^3$, protein 140 mg/L (reference: 150–450 mg/L) and glucose 59 mg/L (reference: 60–80 mg/L). On the fifth day he passed normal stool. Plain abdominal radiograph and ultrasonogram results were normal. He was discharged the next day with a prescription of ceftriaxone for three days.

## DISCUSSION

Rhesus-human reassortant tetravalent vaccine contains three reassortant strains of human serotype G1, G2 and G4 specificity and rhesus rotavirus (RRV) of serotype G3 specificity (18). Reviewing the electropherotype of intussusception causing rotaviruses, a hypothesis has been postulated that wild type G3 human rotaviruses may selectively cause intussusception in infants (19). Therefore, one might consider that intussusception is the particular complication of RRV or serotype G3 rotavirus. Partial support in favor of this view was obtained in a mice experiment. Following oral challenge, RRV was detected in Peyer's patches and mesenteric lymph nodes with greater frequency than the human reassortants (20). However, in the same study, G3 bovine reassortant vaccine strain did not invade the gut-associated lymphoid tissue of the animal model. It was shown in another study that not only RRV but also other rotaviruses are capable of inducing intussusception in a mouse model (3). Therefore, causing intussusception may not be a particular characteristic of RRV or serotype G3 rotavirus. In the present case of intussusception, rotavirus serotype G9P[6] was detected in the stool. It may be assumed from these evidences that intussusception is not restricted to a particular strain or serotype of rotavirus.

The exact mechanism of rotavirus-induced intussusception in humans is not known. In an animal model, it has been demonstrated that rotavirus-induced intussusception does not appear to be mediated by global changes in gastrointestinal transit or hyperplasia of intestinal lymph nodes or Peyer's patches; rather, an inflammatory mechanism has been suggested (3). A study in humans found

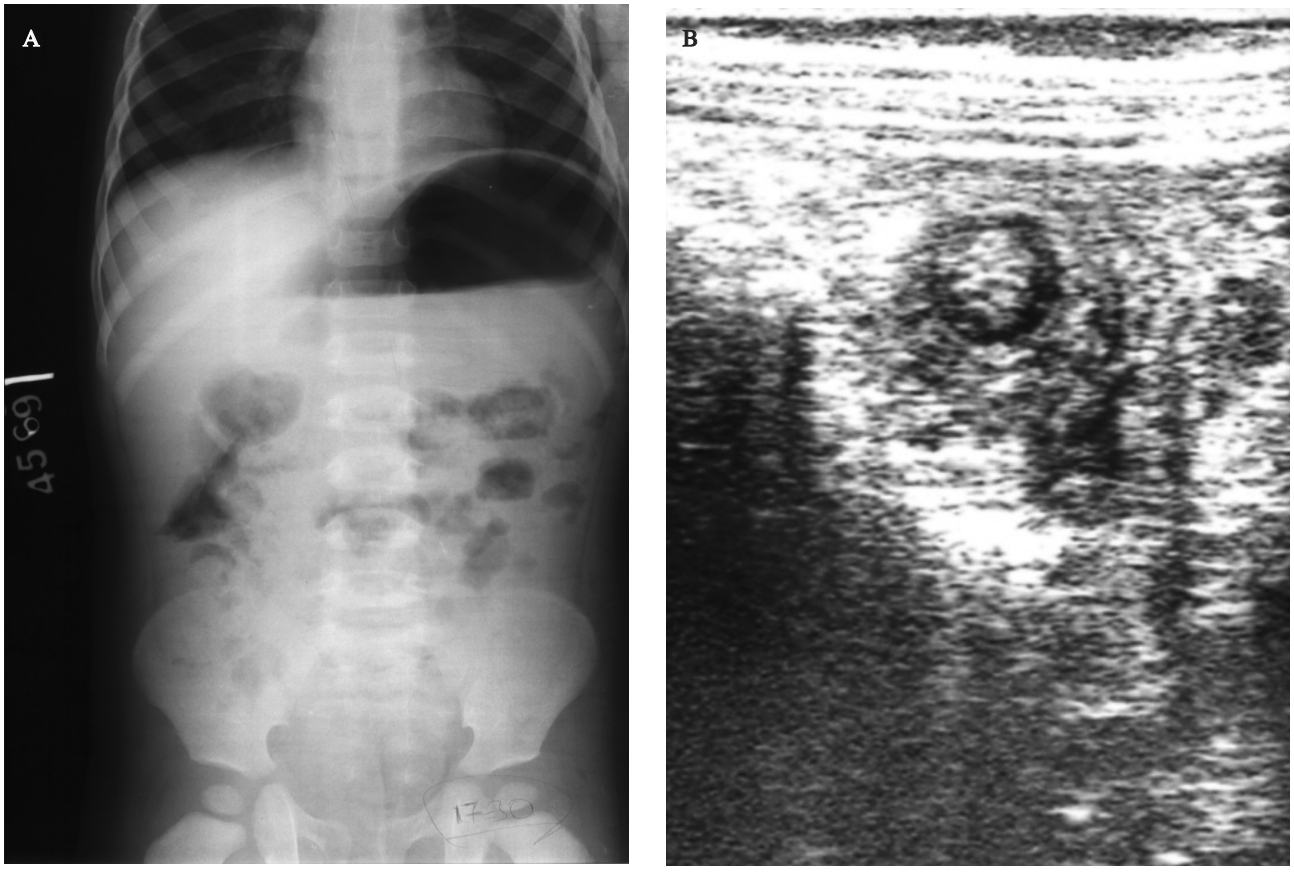


**Figure 1.** X-ray and ultrasonogram of the abdomen. **(A)** Abdominal X-ray showing dilated bowel loops and multiple air-fluid levels. **(B)** The ultrasonogram of the abdomen showing the target sign; the thickened-layered intestine is recognized surrounding the central hyperechoic area, suggestive of intussusception.

that rotavirus infection is associated with increased distal ileum wall thickness and lymphadenopathy during the illness period, and these changes suggest a plausible mechanism by which rotavirus infection could cause intussusception (21). Since the picture of the abdominal ultrasonogram after the alleviation of intussusception was unavailable, the intestinal wall thickness during rotavirus infection could not be determined in the present case. Considering the clinical picture of the patient in this report and the one observed by Robinson et al. (21), rotavirus-associated acute intussusception is possibly transient and frequently resolves without active intervention. This might explain why in several studies there is a general lack of association of rotavirus with intussusceptions.

The CSF of our patient was unavailable for further investigation; therefore, we are not sure whether the patient was at the resolving stage of meningitis or the CSF picture was due to central nervous system (CNS) involvement of rotavirus. There are a number of reports confirming the involvement of the CNS in patients with rotavirus diarrhea (22-24). However, during the course of admission, clinical features suggestive of CNS involvement were not observed.

We have reported here a case of intussusception in a child with natural rotavirus diarrhea. In the present case, two days after the onset of rotavirus diarrhea, the patient developed intussusception and did not pass stool. Since rotavirus shedding ranges from 4 to 29 days following cessation of diarrhea (25), absence of diarrhea in this patient did not indicate that rotavirus was eliminated from the intestine. Therefore, intussusception developed during the period when rotavirus may be found in the intestine. Serotype G9 has been increasingly detected as one of the major serotypes responsible for rotavirus infection worldwide (26); thus far, intussusception has not been reported in these patients. Further studies are therefore needed to determine to what extent the intussusception causing strain of the present case differs from other G9 strains. A recent study concluded that intussusception may more likely be a hyperactive immune response to infectious agents, and children with a general tendency to lymphoid hyperplasia may be at increased risk of intussusception (27). Thus, further studies are also needed to find out whether intussusception during rotavirus infection is regulated by host factors. We present this case as evidence that there is a possibility of an association of intussusception with rotavirus infection. Comprehensive research is needed to obtain further evidence of intussusception associated with natural rotavirus infection and to unravel the dilemma.

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## REFERENCES

1. Del-Pozo G, Albillos JC, Tejedor D, et al. Intussusception in children: current concepts in diagnosis and enema reduction. Radiographics 1999; 19: 299-319.
2. Lam TL. Intussusception. In: Arensman RM, Bambini DA, Almond PS, eds. Pediatric surgery. 1st ed. Georgetown, Texas: Landes Bioscience, 2000; 89-93.
3. Warfield KI, Blutt SE, Crawford SE, et al. Rotavirus infection enhances lipopolysaccharide-induced intussusception in a mouse model. J Virol 2006; 80: 12377-86.
4. Velazquez FR, Luna G, Cedillo R, et al. Natural rotavirus infection is not associated with intussusception in Mexican children. Pediatr Infect Dis J 2004; 23 (10 Suppl): S173-8.
5. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001; 344: 564-72 [Erratum: N Engl J Med 2001; 344: 1564].
6. Konno T, Suzuki H, Kutsuzawa T, et al. Human rotavirus infection in infants and young children with intussusception. J Med Virol 1978; 2: 265-9.
7. Mulcahy DL, Kamath KR, deSilva LM, et al. A two-part study of the aetiological role of rotavirus in intussusception. J Med Virol 1982; 9: 51-5.
8. Nicolas JC, Ingrand D, Fortier B, Bricout F. A one-year virological survey of acute intussusception in childhood. J Med Virol 1982; 9: 267-71.
9. Rennels MB, Prashar UD, Holman RC, et al. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. Pediatr Infect Dis J 1998; 17: 924-5.
10. Bines J, Liem NT, Justice FA, et al.; the Intussusception Study Group. Risk factors for intussusception in infants in Vietnam and Australia: adenovirus implicated, but not rotavirus. J Pediatr 2006; 149: 452-60.
11. Nelson EA, Tam JS, Glass RI, et al. Incidence of rotavirus diarrhea and intussusception in Hong Kong using standardized hospital discharge data. Pediatr Infect Dis J 2002; 21: 701-3.
12. O'Ryan M, Lucero Y, Pena A, Valenzuela MT. Two year review of intussusception in six large public hospitals of Santiago, Chile. Pediatr Infect Dis J 2003; 22: 717-21.
13. Watanabe M, Nakagomi T, Koshimura Y, Nakagomi O. Direct evidence for genome segment reassortment between concurrently-circulating human rotavirus strains. Arch Virol 2001; 146: 557-70.

14. Gouvea V, Glass RI, Fang Z. Polymerase chain reaction amplification and typing of rotavirus nucleic acid from stool specimens. J Clin Microbiol 1990; 28: 276-82.
15. Gentsch JR, Glass RI, Bhan MK. Identification of group A rotavirus gene 4 types by polymerase chain reaction. J Clin Microbiol 1992; 30: 1365-73.
16. Uchida R, Pandey BD, Sherchand JB, et al. Molecular epidemiology of rotavirus diarrhea among children and adults in Nepal: detection of G12 strains with P[6] or P[8] and a G11P[25] strain. J Clin Microbiol 2006; 44: 3490-505.
17. Bines J, Kohl KS, Forster J, et al.; the Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004; 22: 569-74.
18. Bines J. Intussusception and rotavirus vaccines. Vaccine 2006; 24: 3772-6.
19. Nakagomi T. Rotavirus infection and intussusception: a view from retrospect. Microbiol Immunol 2000; 44: 619-28.
20. Moser CA, Dolfi DV, Di Vietro ML, et al. Hypertrophy, hyperplasia, and infectious viruses in gut-associated lymphoid tissue of mice after oral inoculation with simian-human or bovine-human reassortant rotaviruses. J Infect Dis 2001; 183: 1108-11.
21. Robinson CG, Hernanz-Schulman M, Zhu Y, et al. Evaluation of anatomic changes in young children with natural rotavirus infection: is intussusception biologically plausible? J Infect Dis 2004; 189: 1382-7.
22. Goldwater PN, Rowland K, Power R, et al. Rotavirus encephalopathy: pathogenesis reviewed. J Paediatr Child Health 2001; 37: 206-9.
23. Lynch M, Lee B, Azimi P, et al. Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. Clin Infect Dis 2001; 33: 932-8.
24. Salmi T, Arstila P, Koivikko A. Central nervous system involvement in patients with rotavirus gastroenteritis. Scand J Infect Dis 1978; 10: 29-31.
25. Estes MK, Kapikian AZ. Rotaviruses. In: Knipe DM, Howley PM, eds. Fields virology. 5th ed. Philadelphia, Pennsylvania: Lippincott Williams and Wilkins, 2007; 1917-74.
26. Glass RI, Parashar UD, Bresee JS, et al. Rotavirus vaccines: current prospects and future challenges. Lancet 2006; 368: 323-32.
27. Vestergaard H, Westergaard T, Wohlfahrt J, et al. Association between intussusception and tonsil disease in childhood. Epidemiol 2008; 19: 71-4.