Gastroenterology and Hepatology From Bed to Bench.

ORIGINAL ARTICLE

Prevalence of enteric adenovirus and co-infection with rotavirus in children under 15 years of age with gastroenteritis in Qom, Iran

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ABSTRACT

Aim: The current study is the first performed in Qom to determine the prevalence of adenovirus and co-infections with rotavirus in children aged <15 years with gastroenteritis symptoms.

Background: Gastroenteritis-associated viral infections are a cause of death among young children worldwide, especially in developing countries. The Adenovirus species F (40 and 41) are responsible for a range of acute diarrhea cases among infants and children.

Methods: Over a period of 9 months, a total of 130 children suffering from intestinal problems who referred to the infectious ward of Children's Hospital were enrolled in the current study. After clinical examination and collection of demographic information, fecal samples were obtained from the patients. Viral genomes were extracted with a commercial kit and amplified and typed by adenovirus-specific PCR assay. Adenovirus-positive samples were also evaluated for co-infection with rotavirus.

Results: Patients had a mean±SD age of 2.66±2.72 years; 63.1% of patients were male and 36.9% were female. Adenovirus infection was identified in 23 cases (17.7%), 21 (91.0%) and 2 (9.0%) of which were type 41 and type 40, respectively. Fever was the most common clinical manifestation among adenovirus-positive patients. No significant difference was observed between adenovirus infection and clinical symptoms, seasonal pattern, or serum laboratory results. Co-infection was found in only 5 cases (21.7%).

Conclusion: This study was the first to demonstrate adenovirus infection with a relatively high prevalence among children, especially infants, in Qom. The findings further revealed co-infection with rotavirus, indicating a health problem in this region.

Keywords: Adenovirus infections, Rotavirus, Coinfection, Gastroenteritis.

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Introduction

Acute gastrointestinal infections are the second leading cause of death in children, especially those under the age of five years, in developing countries (1, 2). Worldwide, gastroenteritis affects 3 to 5 million children annually, accounts for more than 700 million cases of acute diarrhea every year and 12.0% of all deaths seen in pediatrics up to 2 years of age (3, 4). Viruses, including rotaviruses, enteric adenovirus, norovirus, astrovirus, and calicivirus, are known to be

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the most important etiological agents responsible for about 70.0% of cases of gastroenteritis infection in children (4, 5). Adenoviruses are relatively large, non-enveloped, ds-DNA viruses with >60 recognized serotypes that are grouped into 7 species, A to G (6).

Human adenoviruses (HAdVs) are the cause of common cold or flu-like symptoms and other ailments such as ophthalmic, gastrointestinal, conjunctivitis, hemorrhagic cystitis, exanthema, and urinary tract diseases in humans (7, 8). Adenovirus species F (40 and 41) are responsible for 2.0-23.0% of cases of acute diarrhea among young children, especially infants, and has a higher prevalence in immunocompromised patients (9, 10). These serotypes are mostly associated with gastroenteritis in pediatrics and can be transmitted predominantly via the fecal-oral route (11). Clinical features of enteric adenovirus types 40 and 41 in children include diarrhea, fever, vomiting, abdominal pain, and mild dehydration (12). Compared to other viral infections, adenovirus-induced disease has been reported with prolonged diarrhea (average 10.8 days), acute onset, less frequent vomiting, mild dehydration, and abdominal pain (13).

Infection with more than one microorganism simultaneously, including viruses, virus-bacteria, etc., is known as co-infection (14). Some studies have reported on co-infection of adenovirus with other viruses, including rotavirus, which can be associated with more severe symptoms (15-17). There are also reports on the prevalence and genotype of enteric adenovirus in some parts of Iran (17, 18), but no information is yet available about this virus in Qom. Therefore, the present study aimed to determine the prevalence of adenovirus and co-infection with rotavirus in children aged <15 years experiencing gastroenteritis symptoms in this region. In addition, clinical symptoms, seasonal distribution, and laboratory data were compared in both adenovirus-positive and -negative groups.

Methods

Patients and sample collection

The current work was reviewed and approved by the Medical Ethics Committee of Qom University of Medical Sciences (Code No. IR.MUQ.REC.1394.087). The participants were enrolled in the study after providing the written consent of either the patients or their parents. During a 9-month period, 130 children from the total number of patients who referred to the infectious ward of Hazrat Masoumeh Children's Hospital in Qom, Iran, and had suspected signs/symptoms of viral gastroenteritis were included in the study. The sample size was calculated based on the prevalence estimation formula, according to the prevalence of 20.0% in the Shokrollahi study (19), 5.0% of type I error, and 7.0% precision.

After collecting demographic data, fresh fecal samples were obtained from the patients and immediately transferred to the laboratory. For molecular assessment, a part of each sample was stored at -80 °C until adenovirus/rotavirus polymerase chain reaction (PCR) assay. To evaluate intestinal pathogenic bacteria, the samples were cultured on blood agar, Hektoen enteric agar, xylose lysine deoxycholate agar, and thiosulfate citrate bile-salt sucrose agar, and all were incubated for 48 hours at 37 °C. Other laboratory tests such as white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in serum and also stool examination for WBC, red blood cells (RBC), and ova/parasite were performed. Signs/symptoms from each patient were also documented.

Preparation of stool samples, genome extraction, and PCR

The stool samples were homogenized and treated with chloroform and phosphate buffer saline (PBS) (e.g., ~200 µl of stool, 9 ml of PBS, and 1 ml of chloroform). The mixture was vigorously vortexed for ~20 min. Finally, samples were centrifuged at 2100 g for 20 min at 4 °C (20). The supernatant was directly used for genome extraction using a commercial kit (CinnaPure Viral kit, SinaClon, Iran) according to the manufacturer's protocol. To detect infection and typing of HAdVs, a partial fiber gene of the virus was amplified by PCR. The primers used were AdF1 (5′-ACTTAATGCTGACACGGGCAC-3′) and AdF2 (5′-TAATGTTTGTGTTACTCCGCTC-3′) (21) to produce 541 bp and 586 bp fragments from Ad40 and Ad41, respectively. Adenovirus-positive samples were also evaluated by a conventional PCR using VP6 primers (F: 5′-GACGGVGCRACTACATGGT-3′ and R: 5′-GTCCAATTCATNCCTGGTG-3′) for co-infection with rotavirus. The expected fragment length for detecting rotavirus was 380 bp (22).

PCR reactions were performed in a final volume of 25 µL containing 10 µL of 1X Master Mix (Ampliqon, Denmark), 3 µl of extracted genome, 1 µL of each primer (10 pmol/µL), and 10 µL of sterile deionized water in a thermocycler (Eppendorf, Hamburg, Germany). PCR amplification thermal cycling conditions were as follows: an initial genome denaturation step at 95 °C for 3 min (one cycle), followed by 33 cycles of denaturation at 95 °C for 30 s, primer annealing (adenovirus: 54 °C for 30 s; and rotavirus: 55 °C for 60 s), extension at 72 °C for 30 s, and then a final extension step at 72 °C for 10 min. Finally, the products were electrophoresed on 1.0% agarose gel.

Statistical analysis

Student's t and chi-square tests were used for statistical analysis of the data. The age of patients was calculated as the mean±standard deviation (SD). A p-value <0.05 was considered statistically significant. Statistics were analyzed using SPSS statistics software version 22 (IBM, NY, USA).

Results

Fecal specimens were collected from 130 children with a mean±SD age of 2.66±2.72 years (range: from 1 month to 15 years). Among all patients, 82 (63.1%) and 48 (36.9%) cases were males and females, respectively. Fever was the most common clinical manifestation (63, 48.5%), followed by vomiting (54, 41.5%) and abdominal pain (49, 37.7%).

Adenovirus infection was detected among 23 cases (17.7%), of which 21 cases (91.0%) and 2 cases (9.0%) were determined as type 41 and type 40, respectively. The rate of adenovirus infection was higher in males (18 cases, 22.0%) than females (5 cases, 10.4%) (p=0.096). The age range in positive patients was from 2 months to 9 years (mean±SD age of 2.0±2.37 years). The prevalence was higher for patients <2 years of age (15 cases, 19.5% vs. 8 cases, 15.1%), but this difference was not statistically significant (p=0.520). No significant relationship was observed between the clinical symptoms and adenovirus infection (p>0.05).

After 48 hours, no growth of intestinal bacteria such as *Salmonella*, *Shigella*, or *Vibrio* spp. was observed. All stool samples were negative for the presence of parasites or their larvae. No relationship was found between infection and serum laboratory findings such as WBC, PMN, ESR, and CRP. Compared to adenovirus-negative cases, no RBC in the stool was observed in positive patients. The seasonal prevalence of adenovirus infection was mostly detected in spring and winter seasons, but no significant relationship was observed (p=0.285). More information is summarized in Table 1.

Co-infection of adenovirus and rotavirus was found in only 5 cases (21.7%) of patients. All positive cases were females (100.0%), and their mean±SD age was 4.23±3.52 years (range: from 5 months to 9 years). In the five cases of co-infection, fever (in 80.0% of cases) was the most common symptom followed by vomiting and abdominal pain, each accounting for 60.0% of cases. Most cases of co-infection (60.0%) were detected in the spring.

Table 1. Comparison of clinical symptoms, seasons, and laboratory data in adenovirus-negative and -positive groups

Variable \ Groups	Adenovirus-positive patients (N=23)	Adenovirus-negative patients (N=107)	p-value
Abdominal pain, N (%)	12 (52.2)	37 (34.6)	0.114
Fever, N (%)	13 (56.5)	50 (46.7)	0.394
Vomiting, N (%)	12 (52.2)	42 (39.3)	0.254
Seasonal pattern, N (%)			0.285
Winter	8 (34.7)	21 (19.6)	
Spring	10 (43.4)	58 (54.2)	
Summer	5 (21.7)	28 (26.1)	
WBC, Mean±SD	10656.5217±3526.37	10505.6075±4647.23	0.884
PMN, Mean±SD	50.0870±14.06	55.7850±15.69	0.110
CRP, Mean±SD	19.6826±16.19	24.9028±23.78	0.208
ESR, Mean±SD	19.3043±13.25	22.9159±16.19	0.361
WBC in stool, N (%)	6 (26.1)	32 (30.2)	0.696
RBC in stool, N (%)	0	17 (16)	0.028

Discussion

After rotavirus and noroviruses, adenovirus serotypes 40 and 41 are the most commonly recognized viral agents in infants and young children and are the cause of diarrhea with fever lasting usually for 2 weeks. These serotypes have been estimated to account for 5% to 20% of hospital admissions, depending on economic status or geographic location (23-25). Therefore, infection caused by these viruses is very important in health systems.

To evaluate human adenoviruses directly in clinical samples, species-specific PCRs are better techniques because of their speed, sensitivity, and reliability compared to other methods, such as cell culture and enzyme-linked-immunosorbent assay (ELISA) (26). Therefore, the present study, analyzed samples by PCR to identify adenoviruses.

The isolation rate of Ad40 and Ad41 in the current study was 17.7% and ranged from 2 months to 9 years, indicating a relatively high prevalence of the disease. Studies in other Iranian cities have found lower rates of HAdVs. Motamedifar et al. (2013) found 9.0% in Shiraz (17), Samarbaf-Zadeh et al. (2012) reported 4.3% in Ahvaz (27), and Hamkar et al. (2010) found 2.3% in Mazandaran (28). In Tehran, Damavand et al. (2013), Arashkia et al. (2019), and Modarres et al. (2006) reported HAdV DNA in 2.0%, 4.3%, and 2.6% of patients, respectively (29-31). However, the current results are similar to the results described by Shokrollahi et al. (2014) in a report on HAdVs (20.0%) (19).

The prevalence of the viruses among patients with enteric infections in industrialized countries such as Japan, Australia, and France was 5.0%, 3.1%, and 3.1%, respectively (32-34). In developing countries, however, enteric adenovirus has been reported to be highly variable. The reported rates from Vietnam, Bangladesh, and Thailand were 2.8%, 3.4%, and 3.1% (i.e., 4.4% in children with gastroenteritis and 1.8% in children without gastroenteritis), respectively (34-36), while higher rates were reported from Nigeria (22.3%) (12) and Iran (20.0%) (19). In Iraq, the prevalence of adenovirus is reported at 14.6% (37). Qom is a religious city, and many people from neighboring countries travel to this city; therefore a higher rate of infection is not unexpected.

The current results showed that patients positive for adenovirus infection comprised 22.0% males and 10.4% females. The higher prevalence in males seen in this study is similar to a report published by Sanaei Dashti et al. (male vs. female, 62.8% vs. 37.1%) (18). Conversely, the prevalence of adenovirus in girls with diarrhea was higher in the study of Rezaei et al. (male vs. female, 37.5% vs. 62.5%) (38).

According to the age distribution of children in the present work, the highest incidence of adenovirus was found in children under 2 years of age (15, 19.5%). Other studies have also reported higher prevalence rates of adenovirus in younger children and infants. Sanaei Dashti observed a significantly higher prevalence in children <12 months of age (18). Tang et al. in China indicated that most cases of acute diarrhea in children under 4 years of age were related to HAdV infection (96.67%). They showed the highest infection rate in the age range of 25-36 months (39). Kamal Allayeh et al. also showed a high prevalence of adenovirus in children under two years of age (40).

Although no significant difference was observed, we noted a high frequency of adenovirus infection in spring and winter. The seasonal prevalence was also reported by Motamedifar et al., who found adenovirus to be predominant in July and October (17). In some earlier reports, however, adenoviruses were identified throughout the year with no seasonal pattern or peak of virus infection frequency throughout the year (41).

In the current study, HAdV-41 and -40 contributed to 91% (21 of 23) and 9% (2 of 23) of positive samples, respectively. These findings are similar to those of Kotloff et al. (42), who indicated that Ad41 was more prevalent (68%) than Ad40 (32%). Contrary to the present results, Pereira Filho et al. in 2007 (23) reported Ad40 and Ad41 in 62% and 38% of positive specimens from Brazilian children, respectively. Khoshdel et al. in 2015 (43) also reported that among 100 samples, Ad40 was detected in 14 cases (14%) of Iranian children.

Significant relationships between adenovirus infection and clinical parameters were not found in the current study. Motamedifar et al. (17), however, found a significant result was reported between infection, diarrhea, and fever in patients with adenovirus. They did not, however, find a significant correlation between vomiting, abdominal pain, or other symptoms and adenovirus infection. Furthermore, Akan et al. (44)

found no significant association between clinical symptoms and adenovirus-related infection.

Rotavirus-adenovirus co-infection was determined in 21.7% of cases in the current study, a higher figure than reported by Motamedifar et al. in Iran (4%) (17) and Liu et al. in China (1.11%) (41). It seems that viral co-infections have significantly increased (15). Unlike some previous studies that reported more co-infection in males (17, 45), the current study found co-infection in females to be predominant. Moreover, the clinical manifestations of the disease such as fever, vomiting, and abdominal pain were higher in patients with co-infection than in others. The prevalence of co-infection was more significant in the spring and was similar to reports by Kamal Allayeh et al. in Cairo, Egypt, which stated that spring was the peak season for rotavirus and enteric adenovirus (40).

Conclusion

In summary, the present study is the first of its kind to investigate adenovirus infection in Qom, Iran, and data suggests that a relatively high prevalence of HAdVs could play an important role in diarrheal infections among children, especially infants. In addition, the results showed that co-infections of adenovirus and rotavirus are frequent, indicating a serious problem in our area. This may be due to poor hygiene in some parts of the province, so identifying gastrointestinal viruses in the sewage systems and drinking water sources can be valuable in preventing infections caused by them in the future.

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Conflict of interests

The authors declare that they have no conflict of interest.

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