Original Article

Prevalence of Viruses with Diarrhea among Hospitalized Children West Gyeonggi Province

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Purpose : This study was conducted to evaluate epidemiological data of the viral pathogens obtained from stool exams and provide information on the regional prevalence of infectious diarrheal disease west in Gyeonggi Province, Korea.
Methods : We enrolled a cohort of children <10 years of age admitted for treatment of acute diarrhea at Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea. In total, 310 fecal specimens, documented to be free of common bacterial pathogens, were collected from pediatric patients during a 12-month period from January to December 2009 and were tested for the presence of rotavirus, parechovirus, adenovirus, astrovirus, enterovirus, and norovirus using polymerase chain reaction (PCR) and reverse transcription polymerase chain reaction (RT-PCR) assay.
Results : The most common virus was parechovirus (16%), followed by adenovirus (15%), astrovirus (14%), rotavirus (13%), and enterovirus (5%). Interestingly, only one of the specimens was positive for norovirus. Single infection cases were detected in 173 (55.8%) of the 310 children, whereas mixed viral infections were detected in 10 (3.2%) of the same children. Viral gastroenteritis generally showed a double peak of incidence. Parechovirus, rotavirus, and adenovirus shared a similar pattern of peak incidence with overall viruses; however, astrovirus infections occurred more frequently in the spring. Eighty-five percent of the confirmed viral gastroenteritis cases developed in under 24 months.
Conclusion : The results support the importance of parechovirus, adenovirus, astrovirus, and enterovirus as causative agents of diarrhea in children, which may be underestimated by current routine diagnostic testing. **(Korean J Pediatr Infect Dis 2012;19:28-36)**

Key Words : Parechovirus, Adenovirus, Astrovirus, Rotavirus, Enterovirus, Norovirus

Introduction

Diarrheal diseases remain a leading cause of morbidity and mortality worldwide. The mortality associated with gastroenteritis has been estimated at 4-6 million per year, with most occurring in young children in nonindustrialized countries. The majority of these infections are viral in origin[1-3] and improved diagnostic tools for identifying viruses have made epidemiological features of viral gastroenteritis more clear.

Much of the gastroenteritis in children is caused by viruses belonging to four distinct families; rotaviruses, caliciviruses, astroviruses, and adenoviruses[1, 4].

In the past, human rotavirus was considered responsible for most acute diarrheas in children[5, 6]. In Korea, viral gastroenteritis was mostly attributed to rotaviruses (82.5%), during 2000-2002, followed by adenovirus (2.6%), and astrovirus (0.8%) using

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antigen capture enzyme linked immunosorbent assay [7]. In 2008, Korea Centers for Disease Control & Prevention reported that total viral gastroenteritis detection rate was 23.1% (7,099/30,703) and the most commonly identified viral agent was norovirus which accounted for 12% of the childhood gastroenteritis cases. Rotavirus was 8.3% and enteric adenovirus and astrovirus were 2.1% and 0.6%, respectively[8].

As reported by other investigators, viral excretion was minimal and could not be detected using routine biological tests[9]. While ELISA had been widely used, which is practical, simple and sensitive without irradiation, PCR with higher sensitivity and specificity than electron microscopy or ELISA has been recently utilized and more accurate diagnoses have been made[10-13]. The prevalence and clinical impact of noroviruses continues to expand globally with availability of sensitive molecular diagnostic testing for noroviruses. Currently, noroviruses are considered the leading cause of foodborne diseases and nonbacterial gastroenteritis worldwide[14, 15]. Noroviruses are the second most common cause of severe gastroenteritis in children <5-years-of-age in both developing and industrialized nations, preceded only by rotaviruses. Noroviruses are responsible for 12% of children <5-years-of-age who were hospitalized for severe gastroenteritis worldwide[14, 15]. Recently, parechovirus and enterovirus have been considered agents associated with diarrhea in humans[16-18].

At present, little is known about the current prevalence of parechovirus, enterovirus, norovirus, adenovirus, astrovirus and rotavirus using PCR and RT-PCR in Korea, and there is a need to evaluate the current epidemiological picture of viral gastroenteritis. Therefore, this study was performed to identify viral agents causing infectious diarrhea and to determine their relative significance. Surveillance of the disease, establishment the laboratory diagnosis and providing the information for the measures to prevent the spread of the disease and prophylaxis can be done through an investigation for gender, age, and periodic distribution of gastroenteritis due to rotavirus, parechovirus, adenovirus, astrovirus, enterovirus and norovirus which are commonly found viral agents in Korea.

Materials and methods

We enrolled a cohort of children <10-years-of-age admitted for treatment of acute diarrhea at Bucheon St. Mary's Hospital, the Catholic University of Korea. In total, 310 fecal specimens, documented to be free of common bacterial pathogens, were collected from pediatric patients during a 12-month period from January to December 2009 and were tested for the presence of rotavirus, parechovirus, adenovirus, astrovirus, enterovirus, and norovirus using PCR and RT-PCR.

Preparation of DNA and RNA from stool using QIAamp DNA Stool kit (QIAGEN Inc. Hilden, Germany) and QIAamp Viral RNA Mini kit (QIAGEN Inc.) was performed as follows; Stool samples (180-220 mg fresh or frozen stool) were lysed in lysis buffer. DNA-damaging substances and PCR inhibitors present in the stool sample were adsorbed to a inhibitEX matrix. The inhibitEX matrix was pelleted by centrifugation and the DNA and RNA in the supernatant was purified on QIAamp Mini Spin columns. RT-PCR primers are shown in Table 1. Norovirus, astrovirus, parechovirus, enterovirus,

Table 1. Primers Used for PCR and RT-PCR

Virus	Sequence(5'-3')	Product size (bp)	Reference
Adenovirus	ATG ACT TTT GAG GTG GAT CCC ATG GA	134	16
	GCC GAG AAG GGC GTG CGC AGG TA		
Rotavirus	A1- GGC TTT AAA AGA GAG AAT TTC CGT CTG G	257	16
	A2- GGA CCA AGA GAA AAC GTA GC		
	A4- GGT CAC ATC ATA CAA TTC TAA TCT AAG		
	B1- CTA TTC AGT GTG TCG TGA GAG G	434	
	B3- CGA AGC GGG CTA GCT TGT CTG C		
	B4- CGT GGC TTT GGA AAA TTC TTG		
	C1- CTC GAT GCT ACT ACA GAA TCA G	327	
	C3- GGG ATC ATC CAC GTC ATG CG		
	C4- AGC CAC ATA GTT CAC ATT TCA TCC		
Astrovirus	CCG AGT AGG ATC GAG GGT	88	17
	GCT TCT GAT TAA ATC AAT TTT AA		
Parechovirus	CAC TAG TTG TAA GGC CCA CG	80	18
	GGC CCC AGA TCA GAT CC		
Enterovirus	CCC CTG AAT GCG GCT AAT	154	18
	CAA TTG TCA CCA TAA GCA GCC A		
Norovirus	GI/IIa- ATG TTY AGR TGG ATG AGR TTY T	220	19
	GI- CTT AGA CGC CAT CAT CAT TYA C		
	GI/IIb- ATG TTC CGY TGG ATG CGV TT	90	
	GII- TMG AYG CCA TCW TCA TTC AC		

and group A, B, and C rotavirus sequences were amplied by using coupled reverse transcription and PCR assays. Genotyping for norovirus could show the presence of norovirus genotypes GI and GII. We could detect all 47 human adenovirus serotypes, using the PCR primer pair.

Statistical analyses to compare patients' age and duration of hospitalization (days) among patients with viral gastroenteritis was performed using SPSS (SPSS Inc., Chicago, IL, USA) for Windows and the chi-square test or Fisher's exact tests. A P value <0.05 was considered statistically significant.

Results

In the 310 fecal specimens, viruses were detected in 183 cases, and 195 viruses were isolated. Single viral infections were detected in 173 (88.7%) of the 195 detected viruses, whereas mixed viral infections were detected in 10 (5.1%). The overall rates of prevalence for parechovirus, adenovirus, astrovirus, rotavirus, enterovirus and norovirus were 16%, 15 %, 14%, 13%, 5% and 0.3%, respectively (Table 2). The most frequent dual gastrointestinal infections were rotavirus and astrovirus (30% of 10). Rotavirus was associated with 8 of 10 (80%) mixed infections cases (Fig. 1). Two cases of triple gastrointestinal tract infections were detected.

Viral gastroenteritis showed a double peak incidence. Parechovirus, rotavirus, and adenovirus shared a similar pattern of peak incidence with overall viruses; however parechovirus infection occurred more frequently during autumn (Fig. 2). The peak incidence of astrovirus infection was spring, whereas the peak incidence of enterovirus and norovirus was difficult to describe because of too few cases.

Table. 2. Infecting Virus and Relationship to Gender, Age, and Hospitalization

Characteristic	Type of infection					
	Rotavirus	Parechovirus	Astrovirus	Adenovirus	Enterovirus	Norovirus
No. (%) of children infected	40 (20.5%)	50 (25.6%)	42 (21.5%)	48 (24.6%)	14 (7.3%)	1 (0.5%)
Gender (male)	25	31	27	33	11	1
Age (months)						
Median	14	10	10	12	8	24
Range	2-72	1-69	0-80	1-75	1-30	24
Duration of hospitalization (days)						
Median	6	6	6	6	7	6
Range	1-11	3-13	2-13	3-11	4-11	6

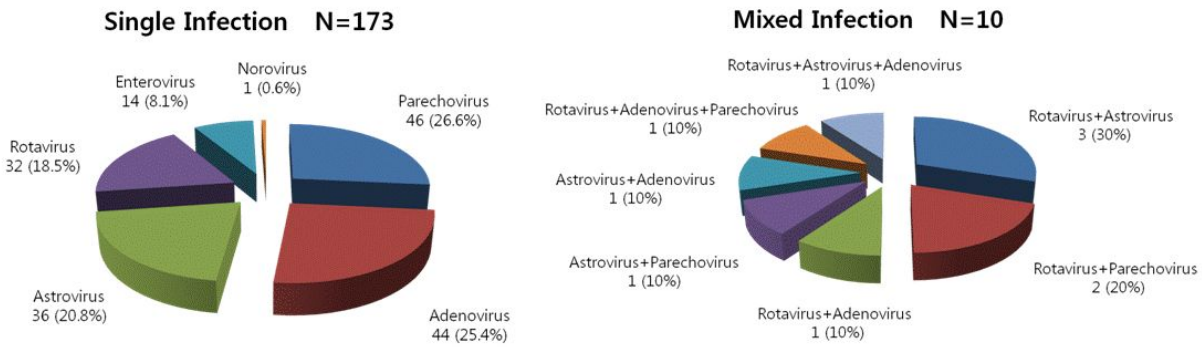

Fig. 1. Distribution of rotavirus-, adenovirus-, astrovirus-, norovirus-, enterovirus-, and parechovirus-positive detection by PCR and RT-PCR among 183 stool samples from hospitalized children in Korea. Distribution (%) of the total number of single (n=173) and mixed (n=10) viral intestinal infections among 310 stool samples from hospitalized children. We identified 55.8% (173/310) of single infections and 3.2% (10/310) of multiple infections.

The clinical characteristics of the children in the study (e.g., gender, age, duration of hospitalization) according to the causative agents are described in Table 2. Median age and duration of hospitalization were not significantly different according to the causative agents. However, 84.6% of the confirmed viral gastroenteritis cases were detected in under 24 months and no case occurred in 7-9 year-old children (Table 3).

Discussion

Acute gastroenteritis is a leading cause of childhood morbidity and mortality in developing countries [1-3]. In this study, we assessed the prevalences of parechovirus, rotavirus, adenovirus, astrovirus, enterovirus, and norovirus in stool samples collected from children hospitalized with gastroenteritis using RT-PCR. This is the first report of an extended study of viral infections and coinfections in hospitalized children in Korea over 12 months.

During epidemic and nonepidemic periods, the predominant viral gastroenteritis agent was rotavirus, particularly in hospitalized children aged 6-18 months. Rotavirus was the major etiologic agent of diarrhea in young children in both developed and undeveloped countries[19]. However, as rotavirus vaccines have become more widely distributed and

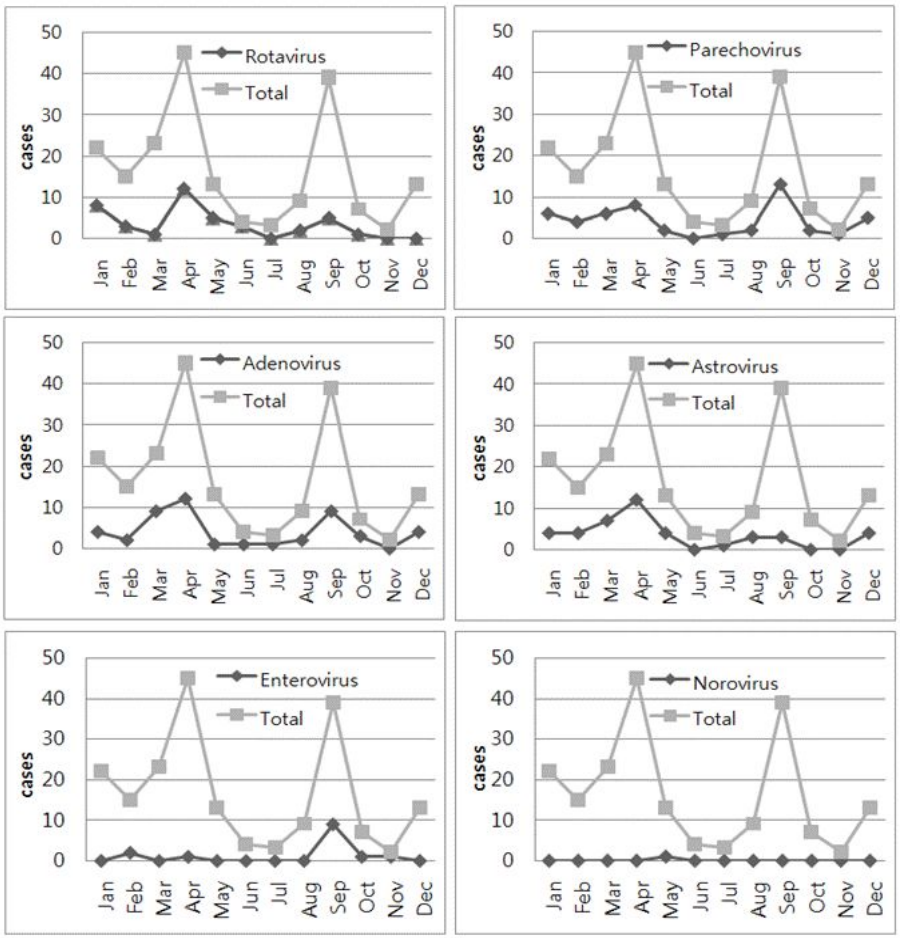

Fig. 2. Monthly distribution of sporadic gastroenteritis cases during 2009.

Table 3. Absolute Frequency of Infection with Different Viruses in Different Age Groups

Age group (months)	Virus						
	Rotavirus	Adenovirus	Astrovirus	Norovirus	Parechovirus	Enterovirus	Total
0–11	14	19	23	0	29	13	98
12–23	18	22	13	0	14	0	67
24–35	1	3	1	1	2	1	9
36–47	4	1	3	0	2	0	10
48–59	0	1	0	0	1	0	2
60–71	1	0	1	0	2	0	4
72–83	2	2	1	0	0	0	5
84–95	0	0	0	0	0	0	0
96–107	0	0	0	0	0	0	0
108–119	0	0	0	0	0	0	0
Total	40	48	42	1	50	14	195

routinely administered in countries such as the U.S., significant decreases in the prevalence of rotavirus infections have been noted[14, 20]. In Korea, a similar change in the prevalence of rotaviral gastroenteritis

has been reported by Korea Center for Disease Control & Prevention. The detection rate of group A rotavirus has decreased from 12.3% (in 2005) to 8.3% (in 2008)[8].

We observed a predominance of parechovirus infections, followed by adenovirus, astrovirus and rotavirus but lower rates of enterovirus and norovirus infections. However, we did not investigate the presence of other recognized enteric viruses, such as sapoviruses, toroviruses, kobuviruses, bocaviruses or aichiviruses, for which molecular detection would probably have significantly increased the overall proportion of documented viral gastroenteritis cases[21]. Investigation of other viruses such sapovirus, torovirus, kobuvirus, bocavirus or aichivirus could help to increase the diagnostic rate in children with gastroenteritis. Moreover, we did not include cases of nosocomial gastroenteritis in our study. Nosocomial diarrhea extends the length of hospital stay and consequently increases the hospitalization costs. Furthermore, a better knowledge of the epidemiology of acute viral gastroenteritis would be valuable for producing an effective vaccine.

While rotavirus had been established for a long time as the major cause of severe gastroenteritis in infants and young children worldwide, norovirus is recently emerging as an important cause of severe gastroenteritis in childhood[22] and has been detected at rates varying between 3% and 30% of hospitalized children, both in developed and developing countries[23-25]. In this study, only one of all specimens was positive for norovirus, which contradicts previous descriptions in Europe[26, 27]. Such variation could be due to different hygienic conditions, different surveillance systems, or to different methods used in diagnostic laboratories in different countries[24]. Norovirus can be divided into at least five genogroups, designated GI-GV, based on aminoacid identity in the major structural protein (VP1)[28]. The strains that infect humans are found in GI, GII, and GV, respectively. On the basis of >85% sequence similarity in the complete VP1 genome, noroviruses can be classified further into genotypes, with at least 8 genotypes belonging to GI and 21 genotypes belonging to GII[28, 29]. Since 2001, GII.4 viruses have been associated with the majority of viral gastroenteritis outbreaks worldwide[30]. Norovirus has also emerged as a major causative agent of epidemic gastroenteritis in Korea[8]. Due to genetic diversity, existing reports are insufficient to represent norovirus infection in Korea[31-33]. Therefore, further prospective multicentric studies are necessary to assess the clinical impact and severity of norovirus gastrointestinal infection domestically.

Previous studies identified mixed infection in percentages ranging from 4.4 to 29% of the pathogen-positive stool samples in different European countries using classic or molecular techniques[3, 27, 34, 35]. In the present study, mixed infections involving two or more viruses were present in 3.2% of tested samples, corresponding to approximately 5.1% of positive viral detection in stool samples. Astrovirus was often present in patients with dual infections[36]. In a large study, the majority of rotavirus infections were combined with adenovirus, calicivirus, or astrovirus[9]. In this study, astroviruses, adenoviruses, and parechoviruses were the most frequently detected viruses implicated in mixed infections in association with rotaviruses.

In this study, no difference in hospitalization duration due to gastroenteritis was found for any infection. However, in previous reports, patients with

mixed infection present with more severe clinical features, and this is possibly due to a synergistic action of multiple pathogens, both in terms of clinical severity and duration of symptoms[6, 37, 38]. These data emphasize the clinical importance of detecting mixed infections as a cause of severe diarrhea in hospitalized children, and more specifically, in those less than 12 months of age. In our study, the few cases of mixed infection made it difficult to identify clinical significance.

Parechovirus was detected mostly in children under 2 years worldwide[39-41]. Norovirus and rotavirus seems to be more prevalent in children <36 months by report of Italy[42]. Similarly, 84.6% of the confirmed viral gastroenteritis cases developed in under 24 months in this study.

The peak incidence of enteric viruses was October to December for norovirus, January to May for rotavirus, and August to October for adenovirus in a study performed in Seoul, Korea[43]. In this study, viral gastroenteritis generally showed a double peak of incidence during spring and autumn. The peak incidence of rotavirus had been generally known as in winter[43, 44]; however, a delay in peak incidence of rotavirus has been reported in some studies[45-47]. In our study, rotavirus showed peaks in January and April, and a small peak in September.

Parechovirus, adenovirus shared a similar pattern of peak incidence with overall viruses; however, astrovirus infections occurred more frequently in spring. The temporal distribution of viral gastroenteritis showed differences between investigators, so more studies will be needed.

In conclusion, our findings provide evidence that parechoviruses are a leading cause of viral gastrointestinal infections and highlight the need to implement parechovirus, astrovirus and adenovirus detection assays in association with rotavirus detection for clinical diagnosis and to assess the clinical impact and the severity of norovirus gastrointestinal infection in the next study.

한 글 요 약

경기서부지역 설사 환아의 바이러스 유병율

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서수영 · 정인아 · 김지훈 · 조경순 · 빈중현 · 김현희 이희진* · 이원배

목 적: 이 연구는 경기서부지역의 감염성 설사의 원인 바이러스의 역학 및 지역적 유병율에 대한 정보 제공을 위해 실시되었다.

방 법: 2009년 1월부터 12월까지 가톨릭대학교 부천성모병원에 급성 설사로 입원한 10세 미만 환아를 대상으로 흔한 세균성 병원체가 없는 310개의 대변 검체에서 rotavirus, parechovirus, adenovirus, astrovirus, enterovirus, norovirus의 유무를 PCR과 RT-PCR을 이용하여 확인하였다.

결 과: parechovirus (16%)가 가장 흔한 것으로 나타났으며, adenovirus (15%), astrovirus (14%), rotavirus (13%), enterovirus (5%)의 순으로 검출되었다. 단일 감염은 55.8%에서, 중복 감염은 3.2%에서 나타났다. 바이러스성 장염은 전체적으로 두 차례의 유행 시기를 보였으며, 84.6%는 2세 이하에서 발생하였다.

결 론: parechovirus, adenovirus, astrovirus, enterovirus는 기존에 시행 중인 진단방법으로는 과소평가되어 있으나 소아 설사의 중요한 원인이다.

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