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The distribution of Rotavirus G and P genotypes in children with acute gastroenteritis in Cukurova region, Turkey

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Abstract

Background: Rotavirus is the major cause of acute gastroenteritis in infants and young children worldwide. The aim of the study was to determine the frequency of rotavirus infection and the distribution of rotavirus G and P genotype combination among children under 5 years of age with acute gastroenteritis in Cukurova region, Turkey, between October 2009 and June 2010.

Material and Methods: The stool specimens (n=846) collected from children with acute gastroenteritis were analyzed by enzyme-linked immunosorbent assay (ELISA) for group A rotavirus antigen. Semi-nested multiplex reverse transcription-polymerase chain reaction (RT-PCR) test was performed for rotavirus G and P genotyping.

Results: The rate of rotavirus infection was found to be in 144 patients (17%). The predominant rotavirus genotype was G1P[8] (22.2%), followed by G1P[4] (17.3%), G2P[4] (13.8%), G9P[4] (6.3%), G9P[8] (4.8%), G2P[8] (2.8%), G1P[10] (2.1%) and G4P[8] (1.4%). The most common G genotype was G1 (41.7%), followed by G2 (16.6%), G9 (11.1%) and G4 (1.4%). Rotavirus P[4] genotype was identified in 37.5%, P[8] in 31.2% and P[10] in 2.1% of samples. The prevalence of mixed rotavirus infections was 29.2% (n=42).

Conclusion: Although the predominant rotavirus genotypes circulating during the study period in our region are targets of current rotavirus vaccines, uncommon, non-vaccine rotavirus genotype combinations such as G1P[4] and G9P[4], which might appear to be the result of mixed rotavirus infections with high rate (29.2%), were also detected. G1 is included in both recent rotavirus vaccines. The continuous investigation of molecular epidemiology of rotavirus infections is essential to evaluate the effectiveness of rotavirus vaccines.

Key words: Rotavirus, Gastroenteritis, Genotypes, ELISA, RT-PCR.

Introduction

Rotavirus is the most common cause of acute severe gastroenteritis in infants and young children worldwide. It is estimated that approximately 600,000 children die annually due to rotavirus gastroenteritis and more than 80% of deaths occur in developing countries. In developed countries, rotaviruses are associated with high morbidity, but low mortality and are the most frequently isolated pathogens in children hospitalized with acute gastroenteritis (1).

The rotavirus belongs to the family Reoviridae, which is non-enveloped with an 11 segmented double-stranded RNA genome surrounded by a triple-layered icosahedral capsid: core, inner and outer capsid. Rotaviruses are divided into seven groups named from A to G, according to the differences in inner capsid protein VP6. Groups A, B, and C rotaviruses infect humans and animals, whereas the D-G groups infect only animals. Group A rotaviruses are the main cause of severe gastroenteritis in children worldwide (2, 3).

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The genes encoding the outer capsid viral proteins VP7 and VP4, which are responsible for cell attachment and entry, allow the classification of group A rotaviruses into G and P genotypes, respectively. Up to now, at least 27 G types and 35 P types have been described for rotavirus group A, but it has been known that only 10 G (G1-G6, G8-G10, and G12) and 11 P (P1, P3-P6, P8-P11, P14 and P19) genotypes infect humans (4). Furthermore, epidemiological studies have shown that five of the G genotypes (G1, G2, G3, G4, and G9) and three of the P genotypes (P1A[8], P1B[4], and P2A[6]) are globally common in humans (1,3,5,6). Another issue that is of critical importance is the emergence of new reassortant virus strains in case of coinfection with different rotavirus strains. There is a large number of G and P genotype combinations circulating in the human population, however five major combinations of G and P genotypes worldwide are G1P[8],G2P[4], G3P[8], G4P[8], and G9P[8] (1,5).

Considering the genetic diversity of rotaviruses, it is advisable to determine geographic variation of predominant strains for effective rotavirus vaccine development. At present, there are two rotavirus vaccines approved in many countries including Turkey, which are Rotarix (GlaxoSmithKline, Research Triangle Park, NC, USA), a live attenuated monovalent vaccine containing rotavirus P1A[8]G1 genotype and RotaTeq (Merck, Rahway, NJ, USA), a live attenuated pentavalent vaccine consisting of G1, G2, G3, G4, and P1A[8] types. However, rotavirus vaccines are not yet included in national immunization programme in Turkey. The efficacy of the Rotarix and RotaTeq against severe diarrhea was found to be 85% and 98%, respectively (3, 7). While deciding the strategy for immunization against rotavirus, it is important to detect the regional incidence of rotavirus gastroenteritis and predominant circulating genotypes before and after immunization.

The aim of this study was to determine the frequency of rotavirus infection and the distribution of rotavirus G and P genotypes among children under 5-years-old with acute gastroenteritis in Çukurova region, Turkey, between October 2009 and June 2010. The results of this study would provide epidemiological information before national implementation of rotavirus vaccines into routine childhood immunization schedule in Turkey.

Material and methods

Sample collection

A total of 846 stool specimens were collected from unvaccinated children with acute gastroenteritis, younger 5 years of age, admitted to Adana Obstetrics and Child Care Hospital from October 2009 to June 2010. The stool samples were stored at -80ºC until tested. Clinical symptoms and demographic data of the patients were obtained via a questionnaire filled out by a physician by face to face interview and after physical examination of the patients.

Rotavirus antigen detection

Stool samples were tested for group A rotavirus antigen using a solid phase sandwich type enzyme immunoassay (Ridascreen rotavirus ELISA test, R-Biopharm AG, Germany). Rotavirus antigen-positive samples were evaluated for rotavirus G and P genotyping by semi-nested multiplex RT-PCR test using the primers previously described by Gentsch et al.,(8) Gouvea et al.,(9) and Iturriza-Gómara et al.(10).

RNA extraction from stool samples

Frozen stool samples were incubated on the bench to dissolve and then diluted 1:10 in phosphate-buffered saline. Viral RNA was extracted using the High Pure Viral RNA Kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions.

RT-PCR for rotavirus G and P typing

The G and P genotyping of rotavirus was performed by using two-step RT-PCR. For rotavirus G genotyping, the 1062 bp fragment of the VP7 gene was amplified with the forward primer Beg9 (5'- GGC TTT AAA AGA GAG AAT TTC CGT CTG G- 3') and the reverse primer End9 (5'-GGT CAC ATC ATA CAA TTC TAA TCT AAG-3'). For P genotyping, the consensus primers Con2 (5'-ATT TCG GAC CAT TTA TAA CC-3') and Con3 (5'- TGG CTT CGC CAT TTT ATA GAC A-3') were used to amplify *VP4* gene fragment of the 876 bp (8-10). For G genotyping, the reaction was carried out with an initial reverse transcription step. Synthesis of cDNA was carried out in 20µl reaction volume by using 10U of reverse transcriptase enzyme (Roche Diagnostics, Mannheim, Germany), 25 pmol of each Beg9, and End9 primers, 20U RNasin (Roche, Diagnostics, Mannheim, Germany), 1mM dNTP mix, 4µl of 5X RT-buffer, deionized distilled water, and 5µl RNA extract, which

were incubated at 55˚C for 30 minute, followed by heating at 85°C for 5 minute to inactivate the enzyme.

The amplification reaction was performed with a 50µl reaction volume consisting of 10X PCR Taq Buffer, 1.5 mM MgCl2, 200 µM dNTP mix, 25 pmol of each Beg9 and End9 primers, 2 U Taq DNA polymerase (Fermentas Life Sciences), and 5 µl cDNA. The thermal cycling conditions were as follows: initial denaturation at 94°C for 3 minutes, followed by 35 cycles of 1 minute denaturation at 94°C, 2 minutes annealing at 42°C, and 1 minute extension at 72°C. The final extension step was carried out at 72°C for 10 minutes. PCR products were analyzed on an agarose gel stained with ethidium bromide and visualized in ultraviolet transilluminator. The same RT-PCR protocol was used for P genotyping of rotavirus with consensus primers Con2 and Con3 amplifying VP4 gene (876bp).

Semi-nested multiplex PCR for rotavirus specific G and P genotyping

Rotavirus specific G and P genotyping was performed using a semi-nested type specific multiplex RT-PCR test that detects seven G types and six P types (8-10). Briefly, in order to identify the specific G type, the amplicons obtained by consensus PCR, type specific primers (G1, G2, G3, G4, G8, G9, and G10) and consensus primer RVG9 for the VP7 gene were used in semi-nested type specific multiplex RT-PCR. For P genotyping, the amplicons obtained by consensus PCR, type specific primers (P4, P6, P8, P9, P10, and P11) and consensus primer Con3A for the VP4 gene were used (8-10). Both G and P genotyping protocols were identical and performed with a 50µl reaction volume consisting of 5 µl of 10X PCR Taq Buffer (100 mM Tris-HCl [pH 8.8], 500 mM KCl), 2 mM MgCl2, 200 µM dNTP mix, 20 pmol of each type specific primers and consensus primer, 2 U Taq DNA polymerase (Fermentas), and 2 µl product of first round PCR. The thermal cycling conditions were as follows: initial denaturation at 94°C for 3 minutes, followed by 35 cycles of amplification (1 minute at 94°C, 2 minutes at 42°C, 1 minute at 72°C for each cycles), and a final extension of 10 minutes at 72°C. All amplified products of G and P genotypes were examined by gel electrophoresis in 2% agarose gel.

Statistical analyzes

The dependent factor in our study was defined as "rotavirus positivity". The independent variables tested were sex, age, symptoms include diarrhea, duration of diarrhea, number of daily bowel movements, vomiting, daily number of vomiting, fever, dehydration, and hospitalization. Chi-square test ($\chi 2$) was used for statistical comparison using EpiInfo 6.0 software. The p-value less than 0.05 were accepted as significant with 95% of confidence**.**

Results

From a total of 846 stool specimens analyzed, 144 (17%) samples were positive for rotavirus antigen. The majority of rotavirus positive cases (71.5%) were under 12 months of age (Table 1). Rotavirus positivity was more frequently observed in age group of 6-12 months among both males ($\chi 2$=15.52; p=0.00043) and females ($\chi 2$=10.86; p=0.0044), in cases with diarrhea lasting 3-4 days ($\chi 2$=12.12; p= 0.00234), with bowel movements of between 6-10 per day ($\chi 2$=17.75; p=0.00014), with vomiting ($\chi 2$=76.45, p<0.0001), with vomiting frequency of 5 or more daily ($\chi 2$=34.27; p<0.0001), in cases with dehydration ($\chi 2$=12.93, p=0.00032), and especially in those with severe dehydration ($\chi 2$=3.14, p<0.0001). In addition, hospitalization was more frequently observed among the children with rotavirus positivity ($\chi 2$=12.83, p<0.001), and rotavirus positive children were 1.96 times more hospitalized [Odds ratio (OR)=1.96 and 95% Confidence Interval (CI)=1.34-2.85]. Rotavirus positivity was not affected by sex ($\chi 2$=0.02; p=0.877), fever presence ($\chi 2$=0.46, p=0.499; Table 1).

According to the monthly distribution of rotavirus infection in children with acute gastroenteritis throughout the study period, higher positivity was observed in December (46 cases, 31.9%), November (25 cases, 17.3%), and January (23 cases, 16%), respectively (Figure 1).

The most prevalent rotavirus genotypes were G1P[8] (22.2%) and G1P[4] (17.3%), followed by G2P[4] (13.8%), G9P[4] (6.3%), G9P[8] (4.8%), G2P[8] (2.8%), G1P[10] (2.1%), and G4P[8] (1.4%) in 144 rotavirus positive cases (Table 2). Among rotavirus positive samples, the most common G genotype was G1 (41.7%), followed by G2 (16.6%), G9 (11.1%), and G4 (1.4%). The most frequently isolated P type was P[4] with the rate of 37.5%, followed by P[8] (31.2%) and P[10] (2.1%). Mixed rotavirus infections occurred in 29.2% (42) of cases (Table 3).

Table 1. Clinical and epidemiological features of children with and without rotavirus gastroenteritis.

Data	Rotavirus positive Number (n=144)	%* (17.0)	Rotavirus negative Number (n=702)	%* (83.0)	*p*-value
Sex					*p*>0.05
Male	79	54.9	393	56.0	
Female	65	45.1	309	44.0	
Age groups (month)					*p*<0.01**
0-5	41	28.5	344	49.0	in both sexes
6-12	*62*	*43.0*	*175*	*24.9*	(with no
13-24	33	22.9	68	9.7	difference
25-36	3	2.1	30	4.3	between sexes
37-48	2	1.4	22	3.1	*p*>0.05)
49-60	3	2.1	63	9.0	
Symptoms					
Diarrhea	144	100	702	100	---
Duration of diarrhea (day)					
1-2	32	22.0	196	28.0	
*3-4***	*58*	*40.0*	*182*	*26.0*	*p*<0.01**
5-7	54	38.0	324	46.0	
Number of daily bowel movements					
3-5	75	52.1	489	69.7	
*6-10***	*65*	*45.1*	*206*	*29.3*	*p*<0.001**
11-15	4	2.8	7	1.0	
Vomiting	*106*	*73.6*	*238*	*33.9*	*p*<0.0001**
Daily number of vomiting					
1-4	47	44.3	174	73.1	
*5-8***	*39*	*36.8*	*55*	*23.1*	*p*<0.0001**
*9-12***	*20*	*18.9*	*9*	*3.8*	
Fever	75	52.1	341	48.6	*p*>0.05
Dehydration	*102*	*70.8*	*380*	*54.1*	*p*<0.001**
Mild	63	61.8	319	84.0	
Moderate	15	14.7	40	10.5	
*Severe***	*24*	*23.5*	*21*	*5.5*	*p*<0.0001**
Hospitalization*	*79*	*54.8*	*269*	*38.3*	*p*<0.001**

*% values are column percentages

**statistically significant independent variables (with the significantly different categories written in italic)

Table 2. Distribution of rotavirus G and P types.

	Number of specimens (%)							
Genotype	**P[4]**	**P[8]**	**P[4]+P[8]**	**P[10]**	**P[4]+P[10]**	**P[8]+P[10]**	**P[4]+P[11]**	**Total**
G1	25(17.3)	32(22.2)	23(16.0)	3(2.1)	-	-	2 (1.4)	85 (59.0)
G2	20(13.8)	4 (2.8)	2 (1.4)	-	-	-	-	26 (18.0)
G9	9 (6.3)	7(4.8)	2 (1.4)	-	2 (1.4)	-	1 (0.7)	21 (14.6)
G4	-	2 (1.4)	-	-	-	-	-	2 (1.4)
G1+G9	3 (2.1)	-	2 (1.4)	2(1.4)	1 (0.7)	1 (0.7)	-	9 (6.3)
G2+G10	1 (0.7)	-	-	-	-	-	-	1 (0.7)
Total	58 (40.2)	45 (31.2)	29 (20.2)	5 (3.5)	3(2.1)	1 (0.7)	3(2.1)	144 (100.0)

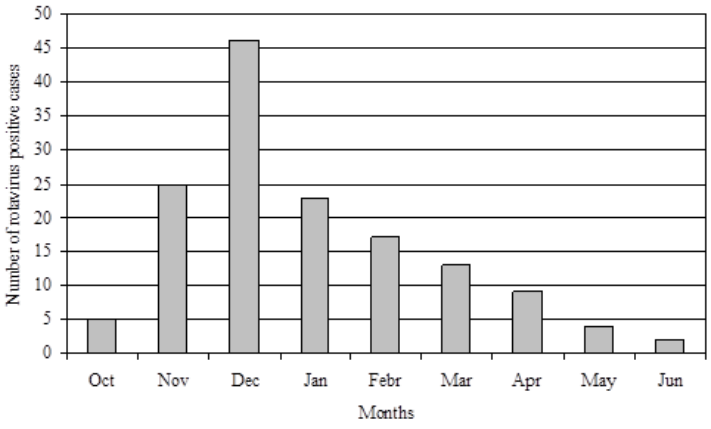

Figure 1. Monthly distribution of rotavirus positive and negative gastroenteritis cases.

Table 3. Distribution of rotavirus G-P genotype combinations of mixed infections.

	Mixed infections	
Genotype combinations	**Number**	**%**
G1/P[4]P[8]	23	16
G1+G9 /P[4]	3	2.1
G2/P[4]P[8]	2	1.4
G9/P[4]P[8]	2	1.4
G1+G9/P[10]	2	1.4
G1+G9/P[4]P[8]	2	1.4
G1/P[4]P[11]	2	1.4
G9/P[4]P[10]	2	1.4
G9/P[4]P[11]	1	0.7
G2+G10 /P[4]	1	0.7
G1+G9/P[4]P[10]	1	0.7
G1+G9/P[8]P[10]	1	0.7
Total	42	29.2

Discussion

The high incidence of rotavirus gastroenteritis in both developed and developing countries suggests that the improvement of personal and public hygiene is not enough to prevent the spread of the disease. Therefore, vaccination is inevitable for prevention against rotavirus infections. Currently, there are two available rotavirus vaccines targeting protection against severe diarrhea, for reducing emergency admission rates, mortality, morbidity, and economic burden due to rotavirus infections (1, 6). Rotarix, monovalent vaccine against P1A[8]G1 genotype, is effective in protection against G1 type (96.4%), heterotypic G types G3 (93.7%), G4 (95.4%), and G9 (85%).13 However, the efficacy of Rotarix vaccine against heterotypic G2P[4] has been reported to be from 41% in Latin America (11), 77% in Brasil (12) to 85.5% in Europe (13).

The rate of rotavirus infection in children with acute gastroenteritis has been previously reported in varying proportions of 13-40.6% in Europe (14, 15), 17-44% in USA, (16, 17) 16-32% in Africa (18), 19.7% in Japan (19), 31.4-52% in China (20, 21), 6.3-35% in India (22) and 12.5-48.9% in Turkey (23-26). The frequency of rotavirus infection in our study was 17% (144 cases). The rates of rotavirus gastroenteritis are comparable in both developed and developing countries, but mortality from diarrhea is greater in developing countries as a result of inadequate treatment (1, 2).

In our study, the most common rotavirus G genotype was G1 with the rate of 41.7%, followed by G2 (16.6%), G9 (11.1%), and G4 (1.4%). The genotype G3, which is also one of the most common types worldwide, was not identified during the study period. Interestingly, the predominant P genotype was P[4] (37.5%), but not P[8] (31.2%). There is limited number of studies conducted on the distribution of rotavirus genotypes in Turkey. Reports in different years from Ankara (24) and Izmir (25) regions in Turkey also showed that G1 was the dominant genotype with 86% and 75.1%, respectively, but being higher than our finding that of 41.7%. We found G2 genotype as the second most common (16.6%) type, was higher than the rates of 3.3% and 0.8% reported in Ankara and Izmir, respectively (24, 25). Higher frequency of G1 genotype has also been consistent with previous results for rotavirus infection in France (61.7%) and Japan (72.7%) (27, 19). Our finding of 41.7% rate for G1 type was similar to that reported from Italy in 2008 (G1 40.7%), however the second most common type observed in Italy was G9, but not G2 (28).

The most prevalent genotype combination in our study was G1P[8] (22.2%) which was also identified as predominant genotype in the previous studies (14,28-30). The other genotypes were found to be G1P[4] (17.3%), G2P[4] (13.8%), G9P[4] (6.3%), G9P[8] (4.8%), G2P[8] (2.8%), G1P[10] (2.1%), and G4P[8] (1.4%), respectively. In contrast with these findings, Çataloluk et al. reported the genotype G4P[8] as the predominant type (42.2%) and G1P[8] as the second most common genotype (26.6%) circulating in Gaziantep region of Turkey in 2005 (31). However, another study indicated that G3P[8] (38.9%) was the most frequent genotype in Ankara from April 2009 to February 2010 (32). As distinct from the other studies (30, 33), the combinations of G genotypes with P[4] represented relatively high frequencies of G1P[4] (17.3%), G2P[4] (13.8%), and G9P[4] (6.3%) in our study. The rates for G1P[4], G2P[4], and G9P[4] genotypes in Europe were 0.29%, 10% and 0.19% respectively (30). The frequency of G9P[8] was 4.8% in our region. Whereas, G9P[8] was detected to be the most common type of rotavirus-associated gastroenteritis in Poland (71.1%) and Spain (87.7%) (14). G9P[8] was reported as the second most common genotype (10.1%) in Istanbul, Turkey (29). Our finding of G2P[8] was 2.8%, while Ittiruza et al. found G2P[8] as 0.47% in Europe (30). The presence of genotype G1P[10] (2.1%), which might be due to possible reassortment between human and animal rotavirus strains, was reported in our study for the first time in Turkey. This genotype was observed in Europe with 1.7%.30 The globally common G1P[8], G2P[4], G4P[8], and G9P[8] genotypes constituted 42.7% of rotavirus strains, but G3P[8], which is also another common genotype, was not detected in our study. The percentage of mixed rotavirus infection in the present study was quite high (29.2%) compared to those reported in previous studies (28-31). These findings confirm that rotavirus genotype distribution varies between regions, countries, and also differs from year to year.

Conclusion

In conclusion, although the predominant rotavirus genotypes circulating during the study period in our region are the targets of current rotavirus vaccines, uncommon, non-vaccine rotavirus genotype combinations such as G1P[4] (17.3%) and G9[4] (6.3%) were also detected. The high rate of mixed rotavirus infections (29.2%) in the study population might increase emergence of new strains due to natural reassortment, which might decrease the effectiveness of current rotavirus vaccines against rotavirus infections. Therefore, continuous prospective monitoring of circulating strains of rotavirus is essential to evaluate the efficacy and convenience of rotavirus vaccines.

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