



Investigation of the Frequency of Rotavirus and Enteric Adenovirus in Children with Acute Viral Gastroenteritis Before and During the COVID-19 Pandemic

Akut Viral Gastroenteritli Çocuklarda COVID-19 Pandemisi Öncesi ve Sırasında Rotavirüs ve Enterik Adenovirüs Sıklığının Araştırılması

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Abstract

Aim: Rotavirus and enteric adenovirus are common causes of acute gastroenteritis in children worldwide. With the emergence of COVID-19 pandemic, measures for pandemic management have also affected frequency of other viral agents. The aim of this study was to investigate changing antigen positivity pattern of rotavirus and enteric adenovirus before and during pandemic and to determine its distribution according to age groups, gender and season of admittance.

Material and Method: Test results of 14670 stool samples of pediatric patients with gastroenteritis between January 2019-June 2021 were evaluated retrospectively. Rotavirus and enteric adenovirus antigens were detected by immunochromatography.

Results: The positivity rates of rotavirus and enteric adenovirus antigen were 9.5% and 1.6%, respectively, before pandemic. A statistically significant decrease was detected for positivity rates of both these viruses during pandemic. Rotavirus antigen positivity significantly increased in 0-2 age group during pandemic (72.9%) compared to pre-pandemic period (70.4%) and significantly decreased from 4.1% to 3.5% in age group of 8-14 during pandemic. Distribution of adenovirus antigen positivity according to age groups did not differ significantly. There was no significant association between period and gender in terms of positivity rates. In pre-pandemic winter, rotavirus and adenovirus positivity rates were found to be significantly higher than in other seasons whereas during pandemic, positivity rates significantly increased in spring and summer.

Conclusion: Frequencies of rotavirus and enteric adenovirus have shown a significant decrease during pandemic. Infection control measures have play an important role in reducing incidence of enteric viruses as well as SARS-CoV-2.

Keywords: Adenovirus, akut gastroenteritis, COVID-19, pandemic, rotavirus

Öz

Amaç: Rotavirüs ve enterik adenovirüs, dünya çapında çocuklarda akut gastroenteritin yaygın nedenleridir. COVID-19 pandemisinin ortaya çıkmasıyla pandemi yönetimine yönelik tedbirler diğer viral ajanların sıklığını da etkilemiştir. Bu çalışmanın amacı, pandemi öncesi ve pandemi sırasında rotavirüs ve enterik adenovirüsün değişen antijen pozitiflik paternini araştırmak ve yaş gruplarına, cinsiyete ve başvuru mevsimine göre dağılımını belirlemektir.

Gereç ve Yöntem: Ocak 2019-Haziran 2021 tarihleri arasında gastroenteritli çocuk hastalardan alınan 14670 dışkı örneğinin test sonuçları geriye dönük olarak değerlendirilmiştir. Rotavirüs ve enterik adenovirüs antijenleri immünokromatografiyle saptanmıştır.

Bulgular: Pandemi öncesi dönemde rotavirüs ve enterik adenovirüs antijeni pozitiflik oranları sırasıyla %9,5 ve %1,6 idi. Pandemi sırasında bu iki virüsün pozitiflik oranlarında pandemi öncesi döneme göre istatistiksel olarak anlamlı bir azalma saptanmıştır. Rotavirus antijen pozitifliği 0-2 yaş grubunda pandemi döneminde (%72,9) pandemi öncesine (%70,4) göre anlamlı olarak artarken, pandemi sırasında 8-14 yaş grubunda %4,1'den %3,5'e düşmüştür. Adenovirüs antijen pozitifliğinin yaş gruplarına göre dağılımı anlamlı farklılık göstermemiştir. Pozitiflik oranları açısından dönem ve cinsiyet arasında anlamlı bir ilişki yoktu. Pandemi öncesi kış mevsiminde rotavirüs ve adenovirüs pozitiflik oranları diğer mevsimlere göre anlamlı derecede yüksek bulunurken, pandemi döneminde ilkbahar ve yaz aylarında önemli ölçüde artmıştır.

Sonuç: Rotavirüs ve enterik adenovirüs sıklığı pandemi döneminde belirgin bir azalma göstermiştir. Enfeksiyon kontrol önlemleri SARS-CoV-2'nin yanı sıra enterik virüslerin görülme sıklığının da azalmasında önemli bir rol oynamıştır.

Anahtar Kelimeler: Adenovirüs, akut gastroenterit, COVID-19, pandemi, rotavirüs



INTRODUCTION

Acute gastroenteritis is an important disease which causes mortality and morbidity during childhood worldwide. Rotavirus is the most common pathogen causing viral gastroenteritis among children younger than 5 years of age especially under 2 years old and enteric adenoviruses are the second one after rotaviruses.^[1-4] Rotaviruses are double-stranded RNA viruses belonging to Reoviridae family and transmitted by fecal–oral route.^[4,5] Human adenoviruses which are double stranded, non-enveloped DNA viruses belong to Adenoviridae family and genus Mastadenovirus. They have 7 types (A to G) and contain over 70 serotypes. Group F serotypes, 40-41, cause gastroenteritis.^[6,7] Adenovirus associated gastroenteritis is transmitted by fecal–oral route similar to rotavirus.^[5]

The COVID-19 pandemic had first appeared in China and spread all over the world in the first months of 2020. The first official case was recorded on 11 March 2020 in Turkey and since then the virus has spread quickly. Therefore, our country and many other countries have taken measures for the management of pandemic.^[8] It has been seen that measures such as frequent hand washing, social distancing, wearing medical masks, decontamination of surfaces, staying at home, closure of schools and travel restrictions reduced the transmission of many viruses other than SARS-CoV-2.^[9-11] In addition, these hygienic measures used to prevent transmission of SARS-CoV-2 have also affected the incidence of viral pathogens that cause gastroenteritis.^[12] In our study, the changing antigen positivity pattern of rotavirus and enteric adenovirus before and during the pandemic was analyzed. Also, the distribution of the frequencies of these viral agents according to age groups, gender and season of admittance was evaluated.

MATERIAL AND METHOD

A total of 14670 stool samples of patients aged 0-18 years who admitted to pediatric outpatient clinics of our hospital with the complaint of diarrhea and tested for rotavirus and enteric adenovirus antigens between January 2019-June 2021 were included in this retrospective study. Test results were analyzed retrospectively from the laboratory information system. Stool samples obtained from patients who had diarrhea as three or more watery defecation within 24 hours were collected in clean and screw-capped containers and transferred to the laboratory within one hour. Analysis were performed as soon as stool samples have arrived to laboratory. Stool samples were firstly examined by direct microscopy for the presence of parasites and cultured on EMB (eosin methylene blue agar) and SS (Salmonella Shigella) agar plates for investigation of Salmonella spp. and Shigella spp. Stool samples that were negative both for parasites on direct microscopy and Salmonella spp/Shigella spp cultures were included in the study. Specimens in leaky containers and transported to the laboratory for more than one hour were excluded from the

study. Rotavirus and enteric adenovirus 40/41 antigens were investigated by qualitative immunochromatography method with combo rapid test (Toyo, Türklab, İzmir, Turkey) according to the manufacturer's instructions.

Statistical Analysis

Data analyses were performed by SPSS (Statistical Package for the Social Sciences) 20.0 (IBM Inc, Chicago, IL, USA). Descriptive measures were presented as mean±SD or median (min-max) for numerical variables and frequency (percentage ratio) for categorical variables. Independent group Student's t-test was used to compare the ages of patients before and after pandemic. Pearson Chi-Square test was used to determine the relationships between categorical information. A $p < 0.05$ value was considered statistically significant by taking at 95% confidence interval throughout the study.

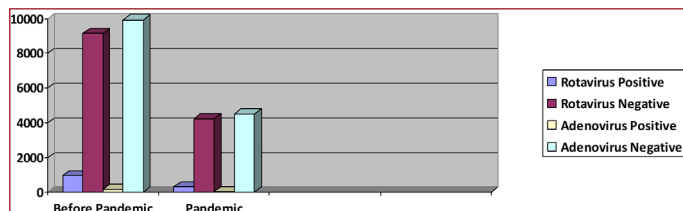
The study was approved by Review Board and Ethics Committee of a University on the date of 01.10.2021 (Ref No: 2021/3424). Informed consent was conducted in accordance with the Ethics Committee and approval procedures.

RESULTS

A total of 14670 samples of patients were included in this retrospective study. The pre-pandemic period has been determined as January 2019-February 2020 and the pandemic period as March 2020-June 2021. Of 14670 patients, 6458 (44%) were female and 8212 (56%) were male. Patients were divided into age groups such as (0-2), (3-7), (8-14) and (15-18). The age group of 0-2 ($n=8468$) comprised the majority of patients with the rate of 57.7%. There were 3737 (25.5%) patients in the age group of 3-7, while age groups of 8-14 and 15-18 consisted of 2085 (14.2%) and 380 (2.6%) patients, respectively. The mean age of patients was $3,78 \pm 0,32$ years (2; age interval: min:0, max:18 years) and there was no significant difference according to gender. It was seen that the mean age increased significantly (3.99 ± 0.06 years) during the pandemic period ($p:0.001$).

It was observed that 68.9% ($n=10104$) of the total of 14670 stool samples were analyzed before pandemic while 31.1% ($n=4566$) of them were analyzed during pandemic ($p < 0.001$). In pre pandemic period, 9.5% ($n=958$) of 10104 of stool samples were positive for rotavirus antigen and 1.6% ($n=160$) of them were positive for enteric adenovirus antigen. During pandemic, rotavirus and enteric adenovirus antigen positivities were found to be as 6.9% ($n=313$) and 0.9% ($n=41$), respectively (**Table 1**) (**Graphic 1**). In a total of 1271 rotavirus antigen positive samples, a statistically significant decrease was detected with the rate of 24.6% ($n=313$) in pandemic period compared to the rate (75.4%) ($n=958$) obtained before pandemic ($p < 0.001$). Likewise, a positivity rate of 20.4% ($n=41$) was obtained for enteric adenovirus antigen in pandemic compared to the rate (79.6%) ($n=160$) obtained in pre-pandemic period ($p:0.001$) (**Table 1**) (**Graphic 1**). While the rate of rotavirus antigen positivity in women was 45.5% before the

pandemic, it decreased slightly to 41.2% during the pandemics. On the other hand, the rate of rotavirus positivity (58.8%) in males obtained during pandemic was higher than the rate found before pandemic (54.5%) (p:0.746). The rate of enteric adenovirus positivity in males (51.2%) increased to 63.4% in pandemic period while the rate of enteric adenovirus positivity in females (48.8%) decreased to 36.6% in pandemic period (p:0.518). There was no significant association between the period and gender in terms of rotavirus and enteric adenovirus positivity (p>0.05) (Table 2).



Graphic 1. Distribution of frequencies of rotavirus and enteric adenovirus during pandemic and before pandemic

The age group of 0-2 included the population with the most frequent pre-pandemic rotavirus and enteric adenovirus positivity rates of 70.4% and 53.8%, respectively. Rotavirus antigen positivity significantly increased in 0-2 age group during pandemic period (72.9%) compared to pre pandemic period (70.4%). However, it significantly decreased from 4.1% to 3.5% in the age group of 8-14 during pandemic (p<0.001) (Table 3). The distribution of enteric adenovirus antigen positivity according to age groups did not differ significantly (p:0.860) (Table 3).

Rotavirus (41.6%) and enteric adenovirus (36.9%) positivity rates were found to be significantly higher in the pre-pandemic winter season than in other seasons (p<0.001). On the other hand, a significant increase was observed in rotavirus and enteric adenovirus positivity rates in the spring and summer months during the pandemic period (p<0.001) (Table 4).

Table 1. Distribution of frequencies of rotavirus and enteric adenovirus during pandemic and before pandemic

	Rotavirus				P*	Adenovirus				P*
	Positive		Negative			Positive		Negative		
	n	%	n	%		n	%	n	%	
Before Pandemic*	958	75.4	9146	68.3		160	79.6	9944	68.7	
Pandemic*	313	24.6	4253	31.7	<0.001*	41	20.4	4525	31.3	<0.001*
Total	1271	100	13399	100		201	100	14469	100	

*:significant at 0.05 level according to Pearson Chi-square test

Table 2. Distribution of frequencies of rotavirus and enteric adenovirus according to gender during pandemic and before pandemic

Gender	Rotavirus								p*	Adenovirus								p*
	Before pandemic				Pandemic					Before pandemic				Pandemic				
	Positive		Negative		Positive		Negative			Positive		Negative		Positive		Negative		
	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%	
Female	436	45.5	3999	43.7	129	41.2	1894	44.5		78	48.8	4357	43.8	15	36.6	2008	44.4	
Male	522	54.5	5147	56.3	184	58.8	2359	55.5	0.746	82	51.2	5587	56.2	26	63.4	2517	55.6	0.518
Total	958	100	9146	100	313	100	4253	100		160	100	9944	100	41	100	4525	100	

*: significant at 0.05 level according to Pearson Chi-square test

Table 3. Distribution of frequencies of rotavirus and enteric adenovirus according to age groups during pandemic and before pandemic

Age groups	Rotavirus								p*	Adenovirus								p*
	Before pandemic				Pandemic					Before pandemic				Pandemic				
	Positive		Negative		Positive		Negative			Positive		Negative		Positive		Negative		
	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%	
0-2**	674	70.4*	5209	57.0	927	72.9*	7541	56.3		86	53.8	5797	58.3	24	58.5	2561	56.6	
3-7	242	25.2	2347	25.6	295	23.3	3442	25.7		51	31.8	2538	25.6	8	19.5	1140	25.2	
8-14**	39	4.1*	1388	15.2	45	3.5*	2040	15.2	<0.001	20	12.5	1407	14.1	9	22.0	649	14.3	0.860
15-18	3	0.3	202	2.2	4	0.3	376	2.8		3	1.9	202	2.0	0	0.0	175	3.9	
Total	958	100	9146	100	1271	100	13399	100		160	100	9944	100	41	100	4525	100	

*: significant at 0.05 level according to Pearson Chi-square test. **:significant at 0.05 level according to pairwise comparison

Table 4. Distribution of frequencies of rotavirüs and enterik adenovirüs according to seasons during pandemic and before pandemic

	Rotavirüs								p*	Adenovirüs								p*
	Before pandemic				Pandemic					Before pandemic				Pandemic				
	Positive		Negative		Positive		Negative			Positive		Negative		Positive		Negative		
	n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%	
Mevsimler																		
Winter**	399	41.6	2713	29.7	78	24.9	648	15.2	<0.001	59**	36.9	3053	30.7	5	12.2	721	15.9	0.012
Spring**	283	29.5	1947	21.3	149	47.6	1413	33.2		29**	18.1	2201	22.1	16	39.0	1546	34.2	
Summer**	82	8.6	2223	24.3	48	15.3	1410	33.2		25**	15.6	2280	22.9	11	26.8	1447	32.0	
Autumn	194	20.3	2263	24.7	38	12.2	782	18.4		47	29.4	2410	24.3	9	22.0	811	17.9	
Toplam	958	100	9146	100	313	100	4253	100		160	100	9944	100	41	100	4525	100	

*: significant at 0.05 level according to Pearson Chi-square test. **:significant at 0.05 level according to pairwise comparison

DISCUSSION

The COVID-19 pandemic has threatened public health and affected the spectrum of infectious diseases worldwide. Many studies indicated that outpatient visits to hospitals for enteric pathogen infections to be analyzed in stool samples during pandemic were significantly less than pre-pandemic period.^[11,13] Similar findings were obtained in our study since 68.9% of the stool samples were analyzed for detection of rotavirus and enteric adenovirus antigens before pandemic but it decreased to about half of it (31.1%) during pandemic.

In studies conducted in Turkey in pre-pandemic period rotavirus antigen positivity rates were found to be as 8.1% in Tokat in 2017 and 11.3 % in Sivas between 2013-2014.^[2,14] A similar positivity rate of 12.7% for rotavirus antigen was obtained in a study conducted in Cyprus between 2015-2018.^[5] These findings were in accordance with the positivity rate of rotavirus (9.5%) obtained in our study before pandemic. A higher positivity rate of 22.4% was reported in a study performed in İstanbul.^[1] Similar positivity rates for enteric adenovirus antigen were reported as 1.8%, 2.6%, 3.1% and 3.2% from Tokat, Sivas, İstanbul and Isparta, respectively.^[1,2,6,14] The positivity rate of enteric adenovirus antigen (1.6%) obtained in our study before the pandemic was paralell with these studies but a study carried out in Cyprus obtained a higher positivity rate of 9.6%.^[5] These differences in positivity rates of rotavirus and enteric adenovirus antigen may be related to selection of different populations, social and economic status of participants and the climatic conditions of regions.

In a study conducted in Korea, the average positivity rates from March 2018 to February 2021 were compared and decreasing rates of rotavirus and enteric adenovirus were reported as 31.8% and 13.4%, respectively. Also, it was emphasized that lifestyle changes such as wearing masks, hand washing and social distance significantly reduced transmission of gastrointestinal viruses as well as SARS-CoV-2.^[15] Similarly, a study conducted in Australia, in 2020, found significant decreases in the incidence of other viruses such as enterovirus and norovirus, and this was explained by the effects of taking measures for COVID-19 pandemic.^[16] In line with these findings, a statistically significant decrease was detected in the positivity rates of both rotavirus antigen (24.6%) and enteric adenovirus antigen (20.4%) during

pandemic compared to pre-pandemic period in our study. It was thought that infection control measures and restrictions applied for the management of the COVID-19 pandemic in our country also contributed to the decrease in the incidence of gastrointestinal viruses such as rotavirus and enteric adenovirus.

It has been shown that rotavirus and enteric adenovirus antigen positivities were common in 0-2 age group in previous studies.^[2,4-6,17] This finding was consistent with data obtained in our study. A study conducted by Li et al. from China differed slightly from these results by showing the highest positivity rates of rotavirus and enteric adenovirus in 1-3 and 3-5 age groups, respectively. Also, it was found that COVID-19 pandemic caused a decline in positivity rates of rotavirus and enteric adenovirus in all age groups except <6 months group for enteric adenovirus.^[13] Contrary to this, in our study, the rate of rotavirus antigen positivity (70.4%) in 0-2 age group significantly increased during pandemic period (72.9%). However, it significantly decreased from 4.1% to 3.5% in the age group of 8-14 during pandemic. In addition, enteric adenovirus antigen positivity did not differ significantly according to age groups and periods. The differences in age distribution may be related with early exposure to contaminated sources in some populations, changing dietary habits according to age and the effects of COVID-19 pandemic on immun system in all age groups.

Many studies conducted before and during pandemic have reported no statistically significant difference in both genders in terms of rotavirus and enteric adenovirus antigen positivity.^[1,3,4,6,11,17] This finding was compatible with our results. Contrary to these, in a study carried out in Cyprus, it was demonstrated that adenovirus positivity was significantly higher in males than in females but there was no statistically significant difference for rotavirus positivity between gender.^[5] Also, Lie et al. reported significantly lower positivity rates for both rotavirus and adenovirus in boys compared to that of girls during pandemic and suggested that the infectious rate may be associated with gender.^[13] These differences may be related to the influence of climacteric conditions and epidemiological characteristics of regions. In addition, the impact of infection control measures for the COVID-19 pandemic may differ between populations in countries.

In recent literature, rotavirus was generally detected in winter whereas enteric adenovirus was seen throughout the year without seasonal association.^[1,2,4,6,7,13] In partially accordance with literature, in our study, rotavirus and enteric adenovirus positivity rates were found to be significantly higher in pre-pandemic winter season than in other seasons. On the other hand, during pandemic, rotavirus and enteric adenovirus positivity rates significantly increased in spring and summer months. The seasonal variation of rotavirus and enteric adenovirus positivity can be related to prevention and control measures of COVID-19 pandemic. These measures can be relieved in spring and summer so the transmission of viruses is much more easier than during winter months.

A study comparing rotavirus activity in winter 2020-21 with winter 2019-20 in Hong Kong reported lower positive rates of rotavirus during pandemic and attributed this decline to both non-drug interventions for global spread of COVID-19 and rotavirus vaccination.^[9] Contrary to this study, Knudsen et al. from Norway reported that enteric adenovirus positivity decreased to the lowest level during pandemic while rotavirus positivity did not significantly reduce due to live attenuated rotavirus vaccine. Rotavirus vaccine has been available in Norway's national immunization programme since 2014 and a stable level of rotavirus positivity has been observed in stool samples due to vaccination during pandemic.^[10] Rotavirus vaccination is a protective factor against infection and recommended by World Health Organization (WHO) in national routine immunization schedules.^[1,4,18] Although rotavirus vaccines have been licensed since 2006, they have not yet been included in the immunization programmes of many countries such as our country. It is a recommended vaccine in our country.^[1,4,9,14,18]

Immunochromatographic method was used for the analysis of rotavirus and enteric adenovirus antigen in stool samples during and before the pandemic in many studies including our study.^[1,2,5,6,13,14,17] This method has high sensitivity and is consistent with the results obtained by ELISA. It also results as quickly as about 10 minutes and can be easily performed on a small amount of stool sample.^[6] Unlike these, in some studies, multiplex reverse transcription polymerase chain reaction has been used and enteric bacteria and virus were simultaneously detected in stool samples of children with acute diarrhea.^[9-11,19]

Our study had some limitations. Determination of rotavirus and enteric adenovirus subgroups and the simultaneous detection of other enteric viruses by molecular diagnostic methods were not performed. The information about rotavirus vaccination history from patients could not be obtained. Despite these limitations, our study includes a notable number of patients and is the first one investigating the frequency of rotavirus and enteric adenovirus in children before and during the COVID-19 pandemic in our region.

CONCLUSION

The frequencies of rotavirus and enteric adenovirus have shown a significant decrease during pandemic compared to the pre-pandemic period. Infection control measures, social restrictions, physical distancing and closure of international borders have play an important role in reducing the incidence of enteric viruses as well as SARS-CoV-2. Whenever these restrictions are relieved, the incidence of many viruses will increase. In addition, detection of rotavirus and enteric adenovirus in children with diarrhea by a reliable, accurate and fast method is helpful for the treatment of gastroenteritis without using antibiotics. The information of frequencies of rotavirus and enteric adenovirus before and during pandemic in childhood will contribute to epidemiologic data in our region.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Review Board and Ethics Committee of Konya Necmettin Erbakan University Meram Faculty of Medicine on the date of 01.10.2021 (Ref No: 2021/3424).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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