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Comparison of Rotavirus Genotypes Before and During the COVID-19 Pandemic

COVID-19 Pandemisi Öncesi ve Pandemi Sürecindeki Rotavirüs Genotiplerinin Karşılaştırılması

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Abstract

Introduction: Rotaviruses are the leading cause of severe diarrhea in infants and young children worldwide. To date, 32 distinct G genotypes and 47 distinct P genotypes have been identified in group A rotaviruses. Following the Coronavirus disease-2019 (COVID-19) pandemic, our country implemented several measures that effectively reduced the incidence of infectious diseases, including acute gastroenteritis associated with COVID-19. In this study, we investigate whether the measures implemented following the COVID-19 pandemic led to changes in the rotavirus genotype distribution.

Materials and Methods: A total of 128 stool samples that tested positive for rotavirus antigen - 64 from the pre-pandemic period and 64 from the pandemic period - were further analyzed for genotyping. As determined by reverse transcription-polymerase chain reaction, rotavirus RNA was detected in 50 (78%) samples from the pre-pandemic period and 51 (80%) samples from the pandemic period.

Results: In the pre-pandemic period, the following results were observed among the patients studied by us: G9P[8] in 24 (48%), G1P[8] in 14 (28%), G2P[8] in five (10%), G2P[4] in three (6%), G3P[8] in two (4%), G4P[8] in one (2%), and G9P[4] in one (2%). During the pandemic period, the following results were observed in the patients studied by us: G9P[8] in 28 (54%), G1P[8] in 12 (24%), G2P[8] in six (12%), G2P[4] in two (4%), G3P[8] in one (2%), G4P[8] in one (2%), and G9P[4] in one (2%).

Conclusion: In our study, G9P[8] was the dominant genotype during both periods, showing no significant difference in rotavirus genotypes between the pre-pandemic and pandemic periods.

Keywords: COVID-19 pandemic, rotavirus, genotype

Öz

Giriş: Rotavirüsler dünya çapında bebeklerde ve küçük çocuklarda şiddetli ishalin önde gelen nedenidir. Bugüne kadar A grubunda 32 farklı G ve 47 farklı P genotipi tanımlanmıştır. Koronavirüs hastalığı-2019 (COVID-19) salgınının ardından, ülkemiz, COVID-19 ile ilişkili akut gastroenterit de dahil olmak üzere bulaşıcı hastalıkların görülme sıklığını etkili bir şekilde azaltan çeşitli önlemler uyguladı. Bu çalışmada COVID-19 pandemisi önlemlerinin rotavirüs genotip dağılımında değişikliğe neden olup olmadığını araştırılması amaçlanmıştır.

Gereç ve Yöntem: Rotavirüs antijeni pozitif olan 64'ü pandemi öncesi ve 64'ü pandemi döneminde olmak üzere toplam 128 gayta örneği genotiplendirme için ileri çalışmaya alındı. Pandemi öncesi dönemde örneklerin 50'sinde (%78) revers transkripsiyon-polimeraz zincir reaksiyonu ile rotavirüs RNA'sı tespit edilirken, pandemi döneminde örneklerin 51'inde (%80) rotavirüs RNA tespit edildi.

Bulgular: Pandemi öncesi dönemde çalıştığımız hastalarda şu sonuçlara ulaşılmıştır: 24'ünde (%48) G9P[8], 14'ünde (%28) G1P[8], beşinde (%10) G2P[8], üçünde (%6) G2P[4], ikisinde (%4) G3P[8], birinde (%2) G4P[8] ve birinde (%2) G9P[4]. Pandemi döneminde çalıştığımız hastalarda şu sonuçlara ulaşılmıştır: 28'inde (%54) G9P[8], 12'sinde (%24) G1P[8], altısında (%12) G2P[8], ikisinde (%4) G2P[4], birinde (%2) G3P[8], birinde (%2) G4P[8] ve birinde (%2) G9P[4].

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Sonuç: Çalışmamızda G9P[8]'nin her iki dönemde de baskın genotip olduğu bulundu. Pandemi öncesi ve pandemi dönemi arasında rotavirüs genotipleri arasında fark olmadığı bulundu.

Anahtar Kelimeler: COVID-19 pandemisi, rotavirüs, genotip

Introduction

Rotaviruses can cause severe diarrhea, especially in infants and children under 5 years. In 2008, it was determined that rotavirus was responsible for 37% of deaths caused by diarrhea in children under 5 years of age. Of all deaths, 5% were caused by rotavirus. It has been reported that over 50% of deaths caused by rotavirus occur in developing countries^[1]. Rotavirus infection occurs in 40% of children under five years who are hospitalized because of diarrhea^[2].

Rotaviruses have a segmented genome containing double-stranded RNA. It is a non-enveloped virus. It has a genome consisting of 11 segments encoding six structural (VP1, VP2, VP3, VP4, VP6, and VP7) and six non-structural proteins (NSP1, NSP2, NSP3, NSP4, NSP5, and NSP6). The group specificity of rotaviruses is based on the VP6 protein (A-E). P serotyping of group A viruses is performed based on the VP4 outer capsid protein, whereas G serotyping is performed based on the VP7 major outer capsid protein, encoded by gene segment 8 or 9^[3].

To date, 32 distinct G genotypes and 47 distinct P genotypes have been identified in group A rotaviruses. Among these, the frequently observed genotypes include six G genotypes (G1, G2, G3, G4, G9, and G12) and three P genotypes. The strains G1P[8], G2P[4], G3P[8], G4P[8], G9P[8], and G12P[8] account for 90% of the group A rotaviruses reported worldwide. Group A rotavirus strain distribution may vary depending on geographical differences and vaccine administration. The number of disease-causing strains is higher in developing countries compared to developed countries^[4].

In response to the Coronavirus disease-2019 (COVID-19) pandemic, various measures have been implemented globally, including in our country. These measures encompass maintaining social distancing, wearing a mask, providing hand hygiene, closing schools, and working from home. These measures have been proven effective in reducing infectious diseases, including acute gastroenteritis and COVID-19^[5,6]. Research has shown that the number of acute gastroenteritis cases caused by rotavirus decreased due to school closures, activity restrictions, and decreased transmission resulting from patients' indifference to seek hospital admission during the pandemic^[5,7].

Information on circulating rotavirus genotypes is essential for guiding vaccine development studies in our country. Therefore, in this study, we aim to investigate the effect of COVID-19 pandemic measures on the rotavirus genotypes in circulation.

Materials and Methods

In this study, two periods were examined: the pre-pandemic period, which spanned from March 11, 2019, to March 10, 2020, and the pandemic period, which spanned from March 11, 2020, to March 10, 2021. For this purpose, stool samples of patients with acute diarrhea and confirmed positive for rotavirus antigen by the immunochromatographic card test were collected from our hospital's microbiology laboratory. The Laboquick Rotavirus-Adenovirus Ag Combo Test (In Vitro Diagnostic Test, İzmir, Turkey) was used to detect rotavirus in stool samples. The rotavirus rapid test cassette features a membrane band that uses red gold-conjugated monoclonal antibodies against the VP6 antigen of group A rotavirus. This test operates on the immunochromatographic principle and solid-phase-specific rotavirus antibodies. Due to the low rotavirus positivity rate during the pandemic period, all rotavirus antigen-positive stools were included in the study. In the pre-pandemic period, rotavirus antigen-positive stool samples were randomly selected to ensure they matched the number of samples collected during the pandemic period.

RNA extraction was utilized in the EZ1 virus Mini Kit (Qiagen GmbH, Hilden, Germany) as described by Durmaz et al.^[8]. VP7 and VP4 gene amplifications were performed using reverse transcription-polymerase chain reaction (RT-PCR) with the specific primers and conditions outlined in the previous study by Durmaz et al.^[8]. VP7 gene amplification was performed using the Superscript One-Step RT-PCR kit (Invitrogen, Carlsbad, CA, USA). For VP4 gene amplification, cDNA synthesis was first performed with a cDNA synthesis kit (Thermo Scientific, Carlsbad, CA, USA). cDNA amplification was performed using the VP4-F/VP4-R primers. G and P genotypes were determined using a seminested multiplex PCR method based on the obtained VP4 and VP7 gene amplicons, employing specific primers as listed in Table 1.

For G typing, PCR was performed using the VP7-R primer along with specific forward primers for G1, G2, G3, G4, G8, G9, G10, and G12. P typing was conducted using specific reverse primer sets for P[4], P[6], P[8], P[9], P[10], and P[11] in combination with the VP4-F primer. Amplified products were analyzed via 2% agarose gel electrophoresis, and G and P genotypes were identified based on their expected sizes^[8].

Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for the Social Sciences statistics version 20 (IBM, USA), with the chi-square test employed to compare categorical variables.

Table 1. Primers used in VP4 and VP7 genotyping

Genes	Forward primer	Reverse primer
VP4	5 'TGGCTTCGCCATTTATAGACA-3'	5 '-ATTTCGGACCATTATAACC-3'
VP7	5 '-ATGTATGGTATTGAATATACCAC-3'	5 'AACTTGCCACCATTTTTC-3'

The study's sample size was determined through power analysis, resulting in 100 participants achieving 95% test power with a 5% error level (G Power 3.1).

Results

In the pre-pandemic period, 2,955 stool samples were sent to our laboratory with a preliminary diagnosis of acute gastroenteritis. Of these, 178 were confirmed positive for the rotavirus antigen. The rotavirus positivity rate was determined to be 6.7%. During the pandemic period, the rotavirus antigen was detected in 64 of the 2,335 stool samples. The rotavirus positivity rate was found to be 2.74%. It was determined that the rotavirus positivity rate decreased significantly during the pandemic period compared to the pre-pandemic period ($p < 0.001$). All rotavirus antigen-positive stool samples during the pandemic period were included in the subsequent genotyping study. In the pre-pandemic period, an equal number of stool samples were randomly selected and included in the subsequent study as those collected during the pandemic period. A total of 128 stool samples positive for rotavirus antigen were included in the further study for genotyping, consisting of 64 samples from the pre-pandemic period and 64 from the pandemic period. Reverse transcription-polymerase chain reaction detected rotavirus RNA in 50 (78%) of the samples from the pre-pandemic period and in 51 (80%) of the samples from the pandemic period. Rotavirus RNA could not be detected in 27 (21%) samples. In the pre-pandemic period, the age range of rotavirus RNA-positive patients was 1-96 months, while during the pandemic period, the age range was 2-105 months. In the pre-pandemic period, 29 (58%) of the patients were male, while 21 (42%) were female. During the pandemic period, 25 (49%) patients were male, and 26 (51%) were female.

Genotyping of rotavirus RNA-positive stool samples from the pre-pandemic period revealed five distinct G genotypes and two distinct P genotypes. Among the G genotypes, G9 was the most common ($n=25$, 50%), followed by G1 ($n=14$, 28%), G2 ($n=8$, 16%), G3 ($n=2$, 4%), and G4 ($n=4$, 1,0%2) genotypes. Among the

P genotypes, P[8] ($n=46$, 92%) and P[4] ($n=4$, 8%) genotypes were detected. Seven different combinations of G and P were identified. The following genotypes were detected: G9P[8] in 24 (48%) of the patients, G1P[8] in 14 (28%), G2P[8] in five (10%), G2P[4] in three (6%), G3P[8] in two (4%), G4P[8] in one (2%), and G9P[4] in one (2%) (Table 2).

Genotyping of rotavirus RNA-positive stool samples from the pandemic period revealed five different G genotypes and two different P genotypes. Among the G genotypes, G9 was the most common ($n=29$, 57%), followed by G1 ($n=12$, 28%), G2 ($n=8$, 16%), G3 ($n=1$, 4%) and G4 ($n=4$, 1,0%2) genotypes. Among the P genotypes, P[8] ($n=48$, 92%) and P[4] ($n=3$, 8%) genotypes were detected. Seven different combinations of G and P were identified. The following genotypes were detected: G9P[8] in 28 (54%) of the patients, G1P[8] in 12 (24%), G2P[8] in six (12%), G2P[4] in two (4%), G3P[8] in one (2%), G4P[8] in one (2%), and G9P[4] in one (2%) (Table 2).

Comparison of genotype frequencies between the pre-pandemic and pandemic periods revealed no significant difference between the two periods (Table 2).

Discussion

Rotaviruses are among the leading causes of acute diarrhea in young children and are associated with high mortality and morbidity rates. It is estimated that rotavirus caused approximately 130,000 deaths and 258 million episodes of diarrhea in children under 5 years in 2016 alone^[9]. The highest death rates were observed in Sub-Saharan Africa, Southeast Asia, and South Asia. In the last decade, the prevalence of rotavirus has decreased worldwide due to public health measures, including improved sanitation and rotavirus vaccine inclusion in the national vaccination programs of over 112 countries. It is estimated that 28,000 rotavirus-related deaths were prevented worldwide in 2016 due to the administration of the rotavirus vaccine^[9]. The incidence of rotavirus decreased from 36% to 13% following the inclusion of rotavirus vaccines in the national program in Italy^[10]. These results demonstrate

Table 2. Rotavirus genotypes in the pre-pandemic and pandemic periods

	G9P[8]	G1P[8]	G2P[8]	G2P[4]	G3P[8]	G4P[8]	G9P[4]
Pre-pandemic period (%)	24 (48%)	14 (28%)	5 (10%)	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Pandemic period (%)	28 (54%)	12 (24%)	6 (12%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)
p value	0.487	0.607	0.775	0.630	0.617	1	1

that vaccination is crucial for preventing rotavirus disease. To evaluate the effectiveness of currently used vaccines or to conduct new vaccine studies, it is essential to understand the circulating rotavirus genotypes.

In countries where the rotavirus vaccine is not administered, rotavirus disease continues to pose a threat to children under 5 years^[9]. In our country, the rotavirus vaccine has not yet been included in the national vaccination program. However, the RotaTeq® (Merck & Co., West Point, PA, USA) and Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) vaccines for rotavirus are available in our country. While Rotarix™ consists of a single human strain G1P[8], RotaTeq® is a human-bovine reassortant vaccine consisting of G1P[5], G2P[5], G3P[5], G4P[5], and G6P[8] strains^[9].

The genotype variations of rotavirus may vary from year to year, depending on factors, such as vaccine administration and geographical region^[6]. In the study conducted by Bonura et al.^[10] in Italy, G1P[8] was identified as the dominant genotype before vaccination, while G2P[4] emerged as the dominant genotype after vaccination. Likewise, in the study conducted by Hungerford et al.^[11] in England, G1P[8] was reported as the dominant genotype before vaccination and G2P[4] after vaccination. The results of these studies demonstrate that the dominant genotypes circulating in society can change with vaccination.

In our country, both rotavirus vaccines are available. However, it is not included in our country's national vaccination program. In the study conducted by Artiran et al.^[12] from 2012 to 2013, which investigated rotavirus genotypes in our country, the most frequently found genotypes were G9P[8] (40%), G1P[8] (17%), and G3P[8] (9.6%). In the study conducted by Bozdayi et al.^[13] in Ankara from 2006 to 2011, G9P[8] (28%) was again found to be the dominant genotype. This was followed by G1P[8] (16.3%) and G2P[8] (15.9%). According to Durmaz et al.'s^[8] study, which covered 23 cities and 35 different centers between 2012 and 2014, the dominant genotype was G9P[8] (40.5%). This was followed by G1P[8] (21.6%) and G2P[8] (9.3%), consistent with the findings from other studies. However, in another study conducted by Durmaz et al.^[14], which covered 20 centers across 15 cities from 2014 to 2016, G1P[8] (24.6%) was identified as the dominant genotype. This was followed by G3P[8] (19.6%) and G9P[8] (12.2%). In a meta-analysis of rotavirus studies conducted in our country, Tapissiz et al. reported a shift in the dominant genotype from G1P[8], which was prevalent between 2001 and 2006, to G9P[8], which emerged as the dominant strain between 2012 and 2018^[15]. Gündeşlioğlu et al.^[16], in their study conducted in Adana from 2013 to 2016, found that the prevalence of G9P8 decreased from 40% to 8.1%, while the prevalence of G1P8 increased from 21.3% to 48.6%. Additionally, G3P8 isolates, which were not observed in the first two years,

were detected at rates of 18.7% and 13.5% in 2015 and 2016, respectively. In Caneriği and Şafak's^[17] studies conducted from 2018 to 2019, the most common genotypes were G1P[4] (44%), G2P[9] (20%), G9P[4] (20%), and G2P[4] (8%). Bulut et al.^[3] conducted a study from 2012 to 2015 in the same region as our study. They identified the most common rotavirus genotypes as G9P[8] (28.9%), G1P[8] (26.5%), and G2P[4] (9.6%). In our study spanning from 2019 to 2020, the most common genotypes were G9P[8] and G1P[8]. Studies conducted in our country have shown that rotavirus genotypes vary from year to year and depend on the region. Furthermore, since the rotavirus vaccine is not included in our country's national vaccination program, not all children are vaccinated. As a result, the dominant genotype may vary depending on the number of vaccinated children in the study cohort. The vaccination information of the patients included in our study is unknown. Therefore, we could not comment on the vaccine's effect on the genotypes.

With the COVID-19 pandemic, various preventive measures were implemented worldwide. In our country, the primary measures included the obligation to wear a mask, restriction on public activities, closure of schools and kindergartens, and online education^[18]. These measures have affected the incidence of other infectious agents in addition to COVID-19. Various studies have shown that rotavirus infection rates, especially common in children under 5 years, decreased significantly during the pandemic period^[5,19]. Roczo-Farkas et al.^[20] reported that the number of rotavirus cases in Australia in 2020 was 18% lower than in 2019 and 27% lower than the average of the previous 5 years. The 2020 annual report from EuroRotaNet, which compiled rotavirus data from 12 European countries, indicated a decline in the number of samples received during the 2019/2020 season compared to previous years^[21]. In our country, Duman et al.^[22] reported that the monthly median positivity rate of rotavirus decreased significantly during the pandemic period. In a study conducted by Alici and Çam^[7] in our country, it was reported that there was a significant decrease in hospital admissions and the number of samples for acute gastroenteritis during the pandemic period. In our study, consistent with previous studies, we found that the rotavirus positivity rate significantly decreased due to pandemic measures.

In our study comparing the rotavirus genotypes from the pre-pandemic and pandemic periods, G9P[8] was the most common genotype in both periods, followed by the G1P[8] strain. The pre-pandemic and pandemic periods had similar rotavirus genotypes. Roczo-Farkas et al.^[20], in their annual report for the Australian rotavirus surveillance program, reported that the G3P[8] genotype was the most common in 2020, accounting for 27% of cases. They stated that the most frequently detected genotype for three consecutive years was G3P[8]. However, the Australian rotavirus annual report for

2021 indicated that the G8P[8] genotype, which accounted for only 1% in 2020, surged to 87.5% in 2021^[23]. In EuroRotaNet's 2020 annual report, which examined a 12-year period, it was reported that G1P[8] was the most common genotype in every season from the 2006/07 season to the 2014/15 season. For the first time in the 2015/16 season, G9P[8] emerged as the dominant genotype, replacing G1P[8]. During the 2019/20 pandemic period, G3P[8] was identified as the dominant genotype, with G1P[8] detected at a rate of 10%. It was also reported that no new rotavirus strains emerged during the 2019/20 season^[21]. This study is the first study conducted in our country to compare rotavirus genotypes from the pre-pandemic and pandemic periods. However, in our study, unlike the aforementioned international studies, the rotavirus genotypes during the pandemic period were found to be similar to those studies observed before the pandemic. This suggests that the pandemic measures did not affect the rotavirus genotypes in our country. This could be attributed to the small sample size and the single-center nature of the study.

Study Limitations

The limitations of this study include its single-center study design and the inclusion of a limited number of samples. Our study is not a prospective study. It is a cross-sectional study.

Conclusion

Our study revealed that G9P[8] was the dominant genotype in both the pre-pandemic and pandemic periods, indicating no difference in rotavirus genotypes between these two times. However, our study was a single-center study with a limited number of patient samples. There is a need for multicenter studies across the country that include a larger number sample size.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Tokat Gaziosmanpaşa University (no: 22-KAEK-106, date: 12.05.2022).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Concept: A.A., M.A., G.Y., B.O., Design: A.A., E.S.T., İ.B., M.A., G.Y., B.O., Data Collection or Processing: A.A., İ.B., M.A., Analysis or Interpretation: E.S.T., B.O., Literature Search: A.A., E.S.T., İ.B., G.Y., Writing: A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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