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Epidemiological Surveillance of Rotavirus and Adenovirus among Patients with Acute Gastroenteritis: A Single-Center Experience in Northern Cyprus

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BACKGROUND/AIMS
The aim of this study was to determine the prevalence of rotavirus and adenovirus in patients with acute gastroenteritis referred to a tertiary hospital in Northern Cyprus and to investigate the distribution of viral infections according to age, sex, and season of the year.

MATERIALS and METHODS
In this retrospective study, a total of 503 stool samples for rotavirus and 490 samples for adenovirus detection from 527 patients were received and examined in the hospital microbiology laboratory between September 2015 and September 2018. A qualitative immunochromatographic rapid antigen test was used for viral antigen screening in stool specimens collected from participants.

RESULTS
In 96 out of 527 patients with acute gastroenteritis in the age group 0–92 years, at least one of the rotavirus and/or adenovirus antigens was detected as positive. Sixty-four (12.7%) of 503 screened patients were positive for the rotavirus antigen, while the adenovirus positivity was detected in 47 (9.6%) of 490 patients. Ten (1.9%) patients were positive for both viral antigens. The positivity of adenovirus was significantly higher in males than in females ($p<0.05$; $p=0.038$). Rotavirus-positive (n=30, 46.9%) and adenovirus-positive (n=31, 66%) cases were identified as the most common in the age group 0–2 years. Both viral antigens were observed most frequently in the summer season (rotavirus, adenovirus: $p>0.05$; $p=0.215$, $p=0.518$, respectively).

CONCLUSION
Acute viral gastroenteritis was most prevalent in the age group 0–2 years among the patients. Rotavirus and adenovirus gastroenteritis could be detected during all seasons in Northern Cyprus, highlighting the importance of rotavirus surveillance particularly in the summer months.

Keywords: Adenovirus, Cyprus, epidemiology, gastroenteritis, rotavirus

INTRODUCTION

Acute gastroenteritis (AGE), characterized by the sudden onset of symptoms, including diarrhea, nausea, vomiting, and abdominal pain, is a major cause of morbidity and mortality worldwide, and it can be life-threatening, particularly for young children in underdeveloped and developing countries. AGE is caused by a range of bacterial, viral, and parasitic pathogens, as well as by toxins, chemicals, and other noninfectious agents. While the implementation of increasing hygiene and preventive measures has significantly reduced the number of cases of bacterial and parasitic AGE, an increase in the frequency of viral infections and outbreaks has recently been observed in Europe and the United States (1, 2). Approximately 1.3 million deaths worldwide are attributed to diarrheal diseases (3). While both community-acquired diarrhea (CAD) and hospital-acquired diarrhea (HAD) are associated with increased health care costs, including treatment

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and hospitalization, in developing countries, rotavirus gastroenteritis alone results in 27 million hospital and outpatient visits and 527,000 deaths among children <5 years of age, with an estimated annual treatment cost of $325 million and total societal costs of $423 million (4).

Gastroenteritis is the second leading cause of infectious-disease-related deaths in children <5 years of age, and viruses are recognized as the most common known agents of AGE (5-7). Among these, adenovirus and rotaviruses are frequently identified as etiological agents of gastroenteritis, and they are responsible for the majority of hospital admissions in infants and children (8). In childhood infections, the etiological agents and severity of the disease vary with age, season, and geographical regions. Therefore, an accurate detection of causative agents in AGE cases is critical in treatment and follow-up.

Rotaviruses are double-stranded RNA viruses, which are transmitted via the fecal–oral route, and they commonly lead to epidemic outbreaks that present with fever, vomiting, and diarrhea, particularly during the winter season. Considered as the most common cause of all severe gastroenteritis in newborns and children worldwide, rotaviruses are responsible for 20%–50% of viral gastroenteritis cases (9, 10). Epidemiological studies show that the percentage of rotavirus gastroenteritis is 20%–40% in Europe, 40%–50% in America, 30%–50% in Asia, and 10%–65% in Africa, while this rate varies between 10% and 40% in Turkey (11-14). Rotavirus gastroenteritis is also associated with a significant economic burden for the health care system, including medical visits, hospitalizations, and treatment costs, as well as for families accounting for the parent work days lost and childcare related costs (15).

Enteric adenoviruses represent other important etiological agents of serious gastroenteritis among infants and young children. Of the 57 identified adenovirus types, only adenoviruses type 40 and 41 were been reported to be associated with diarrhea (16). Adenovirus-induced AGE is spread predominantly by the fecal–oral route and is associated with protracted diarrhea that may contribute to infant dehydration and malnutrition (17). Similar to rotavirus, infection with adenovirus can cause severe disease, increased mortality, and a prolonged hospital stay (18).

The detection of viral gastroenteritis agents is highly important in terms of local epidemiology, monitoring, and surveillance of the disease, which would allow timely implementation of control measures. To the best of our knowledge, there are no data available for the epidemiological surveillance of rotavirus- and adenovirus-associated AGE in Cyprus in the literature. Therefore, in this study, we aimed to screen stool specimens of patients from all age groups, admitted to a tertiary hospital in Cyprus and diagnosed with AGE, for rotavirus and adenovirus antigens, and to determine the prevalence and the distribution of these viruses according to sex, age, and season of the year.

MATERIALS and METHODS

Study Setting

The study was performed at Near East University Hospital in Northern Cyprus. This hospital has 500 inpatient beds and serves about 146,000 outpatients and 6,500 inpatients; approximately 3,000 surgeries are performed annually.

Due to the retrospective nature of the study, no ethical approval was required. The study was conducted according to the Helsinki Declaration. All patient data were anonymized, therefore no informed consent was required.

Specimen Collection

Acute diarrhea is defined as three or more loose or looser-than-normal stools within a 24 h period. Fecal specimens from 527 patients (n=195, 37% inpatients; n=332, 63% outpatients) diagnosed with AGE in the hospital and related clinics between September 2015 and September 2018 were included into this retrospective study. Out of the 527 clinical specimens, 503 were screened for rotavirus, whereas 490 of the stool samples were investigated for the presence of adenovirus as requested by the physician. Demographic features of all cases were recorded. Data from patients who were positive for the presence of parasites in stool microscopy and/or positive for the parasite antigen tests and who were found to be positive for *Salmonella* spp./*Shigella* spp. cultures were excluded from the study. Patients who had diarrheal symptoms at admission or developed diarrhea symptoms within 48 h of admission were considered to have CAD. If symptoms occurred ≥48 h after admission, then HAD was assumed.

Laboratory Virus Antigen Testing

Stool samples were screened using the qualitative immunochromatographic rapid test kit (BioNexia BioMérieux, Marcy-l'Étoile, France) for rotavirus and adenovirus antigen screening according to the manufacturer's recommendations.

Statistical Analysis

Medical records for enrolled study participants were reviewed, and information such as sex, age, date of sample collection, and diagnosis at admission was collected. The distribution analysis of rotavirus and adenovirus prevalence according to gender, age, and season was performed with the Statistical Package for the Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA), using Pearson's chi-square and Fisher's exact tests for statistical analysis. A p-value <0.05 was accepted as statistically significant.

RESULTS

Diarrhea Classification

This study enrolled 527 individuals with diarrheal symptoms. A total of 479 of the cases (90.9%) were defined as CAD, and 48 of the cases (9.1%) were defined as HAD.

Rotavirus and Adenovirus Detection Rates

A total of 527 patients with AGE were included in this study. Patient specimens were subjected to rotavirus (n=503) and adenovirus (n=490) antigen screening. Study participants were in the age group 0–92 years, in which 272 (51.6%) of the patients were males, and 255 (48.4%) were females. While 64 of 503 (12.7%) patients were detected to be positive for rotavirus antigen, 47 of 490 (9.6%) patients were positive for adenovirus antigen. Ten patients (1.9%) showed positive results for both antigens, whereas 96 patients (18.2%) were positive for at least one of the two antigens tested.

Rotavirus and Adenovirus Detection Rates According to Sex

Among rotavirus-positive patients, 38 (59.4%) were males, and

26 (40.6%) were females. In adenovirus-positive patients, 31 (66%) were males, and 16 (34%) were females. The adenovirus positivity was significantly higher in males than in females (p<0.05; p=0.038), whereas no statistically significant difference was observed for rotavirus positivity between males and females (p>0.05; p=0.201) (Table I).

Rotavirus and Adenovirus Detection Rates by Age Group

The median age of study participants was 11.2 (range, 0–92 years). Rotavirus-positive (n=30, 46.9%) and adenovirus-positive (n=31, 66%) cases were most commonly observed in the age group 0–2 years. When cases of viral antigens were evaluated according to age groups, the prevalence of adenovirus was observed to be most frequent in the 0–2 years age group and to be particularly high in the 0–5 years age group, which was statistically significant (p<0.05; p=0.000). On the contrary, there was no statistically significant difference between the age groups of patients for rotavirus positivity (p>0.05; p=0.539) (Table I).

Seasonality of Rotavirus and Adenovirus

Among patients with AGE, both viral antigens were most commonly found during the summer. As shown in Figure 1, 22 (34.4%) of the patients were detected as positive for the rotavirus antigen, and 17 (36.2%) of the patients were detected as positive for the adenovirus antigen in the summer months. Both of the viruses were most frequently observed in June, while rotavirus was equally observed in February. There was no statistically significant difference between the positivity for both antigens with respect to seasonal distribution (rotavirus, adenovirus: p>0.05; p=0.215, p=0.518, respectively). The distribution of viral antigens according to months is shown in Figure 2.

TABLE I. Distribution of the rotavirus and adenovirus positivity according to the age group and sex

Age groups	Rotavirus positivity n (%)	Adenovirus positivity n (%)	Total positive patients n (%)
0–2	30 (46.9)	31 (66)	61 (55)
3–5	12 (18.8)	13 (27.7)	25 (22.5)
6–14	10 (15.5)	2 (4.2)	12 (10.8)
>14	12 (18.8)	1 (2.1)	13 (11.7)
TOTAL	64 (100)	47 (100)	111 (100)
p	0.539	0.000*	
Sex			
Male	38 (59.4)	31 (66)	69 (62.2)
Female	26 (40.6)	16 (34)	42 (37.8)
TOTAL	64 (100)	47 (100)	111 (100)
p	0.201	0.038*	

*p<0.05 significant

DISCUSSION

Diarrheal diseases represent a major health problem, particularly for children in developing countries. Data from a plethora of studies indicate that more than 1 billion children are referred to hospitals due to diarrheal symptoms each year, and approximately 700,000 children lose their lives because of diarrheal diseases (19). Viral gastroenteritis is the leading cause of diarrheal disease representing 30%–40% of all cases reported. Detection of the causative agent of AGE that is viral in origin is critical for an appropriate treatment and implementation of preventive measures. Epidemiological factors such as age, season of the year, and geographic features, in addition to laboratory tests and clinical characteristics, have been proven as useful in differential diagnosis. To the best of our knowledge, this study represents the first epidemiological surveillance report of viral gastroenteritis in Cyprus. In this 3-year retrospective study, the prevalence of acute viral gastroenteritis was found to be 18.2%, providing evidence supporting its importance in childhood diarrhea.

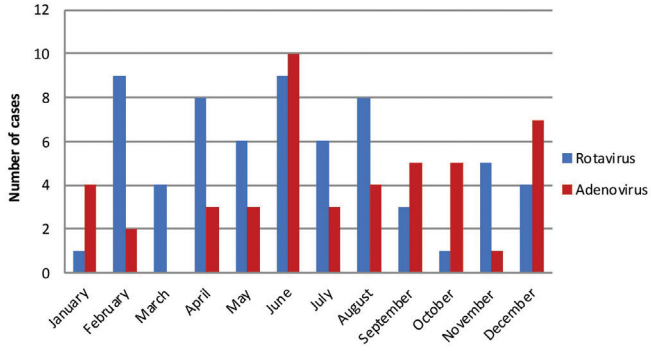

Figure 2. Monthly distribution of rotavirus and adenovirus gastroenteritis

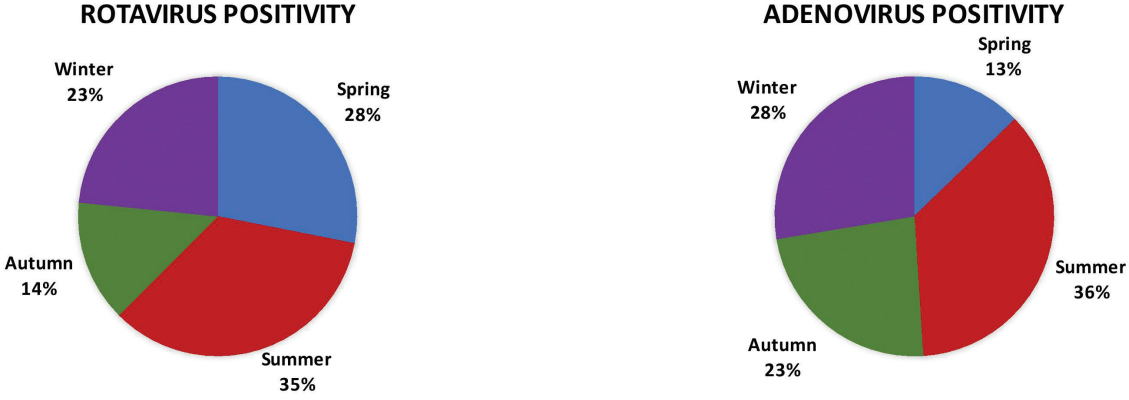

Figure 1. Seasonal distribution of rotavirus and adenovirus positivity

While also commonly seen in adults, rotaviruses and enteric adenoviruses are among the most important agents of viral gastroenteritis in children. Rotavirus-induced gastroenteritis usually presents for 5–8 days with fever and vomiting. The clinical scenario in neonates and children, if not treated, may be fatal due to electrolyte and fluid loss. Although the incidence of rotavirus infections varies according to age and season, they are responsible for 20%–50% of AGE cases worldwide (10, 11). Positivity rates of rotavirus and adenovirus may also vary in different geographical areas due to different detection methods and targeted populations. The prevalence of rotavirus in AGE patients in Turkey during the 2013–2015 period was 14.8% (20). In France and Spain, epidemiological data indicate that the prevalence of rotavirus-associated AGE is 21%. The same incidence is 35% in Italy and 38% in Finland, while in China, the rotavirus positivity among CAD and HAD cases was reported as 22% (21-24). In our study, the incidence of rotavirus gastroenteritis was 12.1% in all CAD and HAD cases investigated in Cyprus, consistent with studies conducted across Turkey.

Adenoviruses are the second leading cause of acute and prolonged diarrhea after rotaviruses. Among them, enteric serotypes 40 and 41 from the subgenus F are most frequently associated with gastroenteritis. Studies from multiple countries indicate that the frequency of adenovirus-induced viral gastroenteritis ranges between 6% and 30%. In England, data collected from 116 UK children confirmed the presence of adenovirus in 12% of cases investigated, while a 5-year study from Ireland indicated the prevalence of gastroenteritis with adenovirus origin at 13.7% (25). In Italy, the rate of detection of enteric adenoviral gastroenteritis in pediatric population was 23% (26). In a pediatric ward in Iran, the adenovirus positivity in children aged <5 years was reported to be 14% and 8%, for adenovirus serotypes 40 and 41, respectively (27). Similarly, in one of the first reports on enteric adenoviruses in India, data from three different cities and 439 hospitalized patients revealed the virus incidence as 7%–9% (28). In a study by Qui and colleagues (29), the adenovirus positivity was detected in 79 (28.9%) of 273 children with diarrhea, including seven different serotypes (human adenovirus 40, 41, 3, 2, 1, 5, and 57) in China. On the other hand, a marked decrease in rotavirus detection was observed among unvaccinated preschool children in the Netherlands during the rotavirus season (January–April), where the rates of positivity were as low as 0.6% in 2014 compared to 11.2%, 6.9%, 6.8%, and 6.7% in 2010, 2011, 2012, and 2013, respectively (30). When pediatric age groups are evaluated, epidemiological data from Turkey demonstrated that the highest viral antigen positivity in children 13–24 months of age was 24.5% and 8.2% for rotavirus and adenovirus, respectively (20). In the study conducted by Hamkar et al. (31), it was shown that the rotavirus positivity was most frequently seen in the group aged <1 year, while the adenovirus positivity was detected predominantly in the age group 2–5 years. In our study, the prevalence of adenovirus in children aged 0–5 years was 12% (n=44/352), 1.9% (n=3/138) in cases older than 5 years, and 9.6% (n=47/490) in all age groups. Consistent with previous reports, our data suggest that adenoviruses are more frequently seen in children aged 0–5 years.

When previous studies on the association of demographic data and incidence of rotavirus and adenovirus gastroenteritis were analyzed, no statistically significant relationship was found between the two viral antigens and gender (32-34). In our study, there was no statistically significant relationship between rotavirus gastroenteritis and gender, whereas adenovirus gastroenteritis was significantly higher in males. Similarly, a number of previous studies reported that adenovirus gastroenteritis is more common in males (34, 35), although a few reports indicated no statistically significant association between adenovirus gastroenteritis and gender (36, 37).

The seasonal distribution of rotaviruses is well known. Global surveillance studies show that rotaviruses are the leading cause of gastroenteritis, typically starting in autumn and continuing during the winter months with a peak of viral gastroenteritis hospitalizations in the winter. In their landmark study, Cook et al. (38) demonstrated that rotaviruses had a distinct seasonal peak in countries with temperate climates but were seen year-round in the tropical setting. A large cohort study in hospitalized pediatric patients in Germany indicated that rotavirus infections are most frequently observed from January to April, while adenoviruses were detected mainly in December with a second peak in March (39). Although adenovirus infection rates are similar in every period of the year, there is a trend of statistically insignificant increase in summer months. In the study by Bicer et al. (40), it was emphasized that summer was the peak season for enteric adenovirus infections, with July (17.3%) and August (20.9%), having the highest incidence rates. Our results indicate that both viral gastroenteritis agents were most commonly detected in the summer, although this was not statistically significant. Due to the Cyprus climate, which is hot in the summer and mild with low rainfall rates in the winter, the viral pathogens can be found at similar rates during different seasons. Data obtained in this study highlight that the surveillance of rotavirus gastroenteritis in summer months is of critical importance. The number of patients included in this study and the lack of screening for both viral antigens in each patient sample were among the limitations of this study.

To the best of our knowledge, this study represents the first report of epidemiological characteristics of rotavirus- and adenovirus-associated AGE in Cyprus. AGE associated with the viral pathogens studied was most commonly observed in the age group 0–2 years, whereas both agents were responsible for enteric infections in other age groups. Our findings highlight that rotavirus and adenovirus infections can be seen among patients with AGE during all seasons on the island, with adenovirus infections being more frequently observed in males. In summary, we conclude that the early diagnosis of viral pathogens in patients with AGE and the implementation of a multicenter surveillance system in Cyprus will prevent severe disease manifestations and would allow rapid and more effective prevention strategies.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Due to the retrospective nature of the study, informed consent was not required. Patient data were anonymized.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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