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Prevalence of Human Adenovirus, Epstein-Barr Virus, and Cytomegalovirus in Pediatric Hematologic Diseases in Iran

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ABSTRACT

Background: Gastroenteritis is the second leading cause of death worldwide, with a high prevalence in children. Among pathogenic microorganisms, viruses are one of the main causes of this disease. Thus, the aim of this research was to investigate the prevalence of diarrhea caused by human adenovirus (HAdV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) in children with hematological diseases for the first time in Iran. .

Materials & Methods: This study was conducted on 120 stool samples stored in the clinical sample bank of the Cellular and Molecular Research Center of Qom University of Medical Sciences. These samples were obtained from immunocompromised children with gastrointestinal symptoms, who referred to one of the children's hospitals in Qom during 2018 to 2019. Genomes were extracted from the stool samples and evaluated using the polymerase chain reaction (PCR) method.

Findings: The prevalence of HAdV and EBV was reported in seven (5.8%) and one (0.8%) cases, respectively, and CMV was detected in none of the samples. No cases of co-infection were observed.

Conclusion: This study results show that there are diarrhea-causing viruses among patients in the study area. Fortunately, the prevalence of these infectious agents in patients with underlying conditions was relatively low. However, monitoring of these viruses in the feces of all patients, especially immunocompromised patients, is recommended.

Keywords: Adenoviruses, Epstein-Barr virus, Cytomegalovirus, Hematologic diseases, Polymerase chain reaction, Children

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Introduction

An average of three billion cases of infectious diarrhea caused by microorganisms, including bacteria, viruses, and parasites, occur annually worldwide, mainly in children under 5 years of age [1]. In addition, this disease is a common problem, especially in patients with immunocompromising conditions. Compared with healthy hosts, these cases are mainly at risk of severe gastrointestinal infections, which are associated with significant morbidity and mortality worldwide [2-9]. According to reports, viruses are responsible for a significant proportion of all acute diarrhea cases (30-40%) [10].

Human adenoviruses (HAdVs) are non-enveloped, double-stranded DNA viruses belonging to the *Adenoviridae* family [11]. Along with respiratory infections, HAdVs also cause diarrhea in patients, especially in children [12]. These viruses could cause fatal infections in newborns and immunocompromised patients. Since they multiply effectively in the intestine and are excreted through feces, they play an important role as infectious agents in causing diarrhea [13, 14]. Studies conducted in Iran have reported a prevalence of 2.3 to 20.0% for HAdVs infections [15-19]

Epstein–Barr virus (EBV) belongs to the *Herpesviridae* family and has a double-stranded DNA, which infects more than 90.0% of the world's population [20]. In a seroprevalence study in an Iranian city, the prevalence of EBV ranged from 70% in children to more than 90% in adults [21]. EBV is strongly involved in the pathogenesis of Hodgkin's lymphoma, Burkitt's lymphoma, and esophageal and gastric cancers, and rarely in gastroenteritis. However, although certain primary infections in the first years of life or adolescence are asymptomatic or the result of mononucleosis infection, the virus has been shown to cause benign or malignant gastroenteritis in some cases [22-24]. Cytomegalovirus (CMV) also belongs to the *Herpesviridae* family and has a double-stranded DNA. The virus affects 40-100% of the world's population [25]. This virus is the predominant infectious agent of congenital birth defects and an opportunistic pathogen in immunocompromised patients. After the retina, the colon is the most common organ affected by CMV in these people [26]. CMV is one of the serious and rare agents in the gastrointestinal tract of cancer patients who are treated with drugs that weaken the immune system [27].

Acute lymphocytic leukemia (ALL) is a common malignant hematologic disease (i.e. malignancy of B or T lymphoblasts) characterized by uncontrolled proliferation of abnormal and immature lymphocytes and their progenitors. The incidence rate of the disease is closely related to age and gender and is ~ 3.3 cases per 100,000 children [28, 29]. Non-Hodgkin's lymphoma (NHL) is a diverse and heterogeneous group of malignant neoplasms originating from lymphoid tissues, mainly lymph nodes. The incidence of NHL has been increasing rapidly worldwide over the past few decades [30, 31]. Considering that the focus of research on cancer patients has been more on therapeutic, epidemiological, genetic, and immunological aspects, the assessment of infection in these patients has received less attention, and there are not many reports of them in the study area.

Objectives: The aim of this study was to investigate the presence and prevalence of these viruses causing gastrointestinal infections in patients with underlying conditions for the first time in Iran.

Materials and Methods

Samples: This research was conducted on 120 stool samples stored in the clinical sample bank of the Cellular and Molecular

Research Center of Qom University of Medical Sciences. Briefly, the samples were collected from immunocompromised patients who were undergoing chemotherapy for ALL and NHL and had symptoms of diarrhea and referred to one of the reference children's hospitals in Qom during 2018 to 2019. Overall, inclusion criteria included prior informed consent obtained from the children's parents/guardians and the presence of a hematological disorder and symptoms of infectious diarrhea. At the time of sample collection in the hospital laboratory, the culture of intestinal bacteria (mainly *Salmonella* and *Shigella* species), the presence of protozoa and/or ova of parasites, as well as other stool-related tests were investigated.

Nucleic acid extraction and polymerase chain reaction (PCR): According to the manufacturer's instructions, viral genomes were extracted by a viral nucleic acid extraction kit (YTA, Iran). All samples were tested for the presence of HAdV, EBV, and CMV. The target regions of the genes were amplified in a final volume of 25 µL, including 10 µL of 1X Master mix (Ampliqon, Denmark), 1 µL of each primer (10 pmol/µL) (Table 1), 3 µL of extracted DNA (50 ng), and 10 µL of distilled water. The following cycles were performed: one cycle for denaturation (at 94 °C for 10 min), followed by 40 cycles for amplification (at 94 °C for 45 s), annealing (at 55 °C for 45 s), and extension (at 72 °C for 45 s), and a final cycle for extension (at 72 °C for 10 min). Genomes of positive clinical samples available in our laboratory were used as positive controls in PCR. PCR products were analyzed by electrophoresis.

Statistical analysis: The findings were reported using descriptive statistics including m±SD (mean±standard deviation) as well as frequency and frequency percentage. In addition, the relationship between patient's symptoms, infection rate, and their comparison with other qualitative demographic variables was considered by Fisher's exact test and chi-square test. Statistical analysis was performed in SPSS 22 software (IBM, NY, USA). A *p*-value of less than 0.05 was considered statistically significant.

Findings

The patients' age range was from 7 to 192 months with a mean±SD age of 59.37±40.03 months. Among the patients, 98.3% had bloody diarrhea (118 of 120), and fever, anorexia, vomiting, weight loss, and abdominal cramp were the most common symptoms. Overall, PCR results were positive for eight out of 120 (6.7%) patients: seven (5.8%) cases for HAdV and one (0.8%) case for EBV. The mean age of HAdV-positive patients was 77.71±52.16 months (ranging from 9 to 156 months). The EBV-positive patient was an 18-month-old boy. Most HAdV-positive cases (71.4%) and one EBV-positive patient (100.0%) were in the ALL group. There was no a significant correlation

Table 1) List of primers used in this study

Virus	Primer Sequences (5'→3')	Size (bp)	Reference
HAdV	F- GCCGCAGTGGTCTTACATGCACATC R- CAGCACGCCGCGGATGTCAAAGT	300	[32]
EBV	F-ACAGCTAGCAGACATTGGTGT R-CCTGTCATTTTCAGATGATTTGG	430	[33]
CMV	F- CACCTGTCACCGCTGCTATATTTGC R- CACCACGCAGCGGCCCTTGATGTTT	400	[34]

between different variables and infection with these viruses. No co-infections were also detected among the positive patients. In addition, all subjects were negative for CMV infection.

Moreover, the most samples were collected in the autumn season (87 of 120). This showed that the highest incidence of diarrhea occurred in this season, but it was not statistically significant (p = 0.53). According to the season variable, five HAdV-positive cases (71.4%) and one EBV-positive case (100.0%) occurred in autumn. However, there was no significant relationship between season and positive cases of infection. More information is provided in Table 2.

Discussion

Diarrhea caused by microorganisms is the most common disease among patients [35-39], especially in children. The disease is the second leading cause of death, accounting for about 10.0% of deaths worldwide. Among infectious agents, viruses are responsible for a significant proportion of acute diarrhea cases, and various reports on the prevalence of viral diarrheal diseases have been published in developing and developed countries [18, 38, 40, 41]. Several risk factors influence the incidence and severity of viral diarrheal infections, including poor hygiene, immunocompromised conditions, transplantation, etc. [42, 43].

In this study, 101 patients with ALL and 19 patients with NHL were included. ALL is the most common malignancy in children, which makes them susceptible to various infections, especially opportunistic ones [44]. NHL is a malignant monoclonal proliferation of lymphoid cells. Opportunistic infections in patients with NHL are of interest to both physicians and microbiologists [45, 46].

Many studies have been conducted in the world on three viral agents, including HAdV, EBV, and CMV, but there are few studies on their prevalence in people with specific underlying diseases. According to this study results, a total of eight patients were positive for the investigated viruses, indicating a low prevalence similar to other studies results. In a 10-year retrospective study (2005-2015) of immunocompromised and cancer patients in the USA by Ghosh et al. (2017), a total of 97 viral diarrhea cases were identified [47].

In this study, HAdV was detected in seven cases: six cases in the ALL group and one case in the NHL group. Adenovirus infections have spread globally, and different prevalence rates have been reported for them even within a country. For example, their prevalence in China was reported to be 4.44% in Chongqing during 2017–2019 [48] and 9.8% in Beijing during 2011-2012 [49]. In Iran, Sanaei Dashti et al. (2016) reported a prevalence of 5.18% for adenovirus infections in stool samples collected from five cities during 2012-2013, including Tehran, Shiraz, Mashhad, Tabriz, and Bandar Abbas [50], while Shokrollahi et al. (2014) reported a prevalence of 20.0% in Tehran during 2009-2011 [19]. In our previous study, the prevalence of adenovirus was 17.7% among pediatric gastroenteritis patients in Qom [18]. Similarly, Durepaire et al. (1995) reported that 8.7% of HIV-positive patients were also positive for adenovirus [51]. Schofield et al. (1994) also reported a case of adenovirus-induced gastroenteritis in a patient with chronic lymphocytic leukemia [52]. In a study conducted by Ribeiro et al. (2015) in Portugal on immunocompromised patients diagnosed with different hematological malignancies and acute diarrhea, adenovirus prevalence was reported as 12.4% [53]. There are various reports of infections caused by this virus in the early months after transplantation [54, 55].

The prevalence of EBV and CMV ranges from 60 to 100% among the world's population[56]. After primary infection, these

Table 2) Information about gender, age, season, clinical symptoms, and hematological diseases of HAdV- and EBV-positive patients and comparison with negative patients

Parameters		Patients	HAdV-Positive Patients (N=7)			EBV-Positive Patients (N=1)			Negative Patients (N=112)		
		No.	%	*p*-value		No.	%	*p*-value	No.	%	*p*-value
Gender	Female	2	28.6	0.70		0	0.0	-	46	41.1	0.31
	Male	5	71.4			1	100.0		66	58.9	
Age (year)	0-4	2	28.6	0.42		1	100.0	-	58	51.8	0.62
	5-8	3	42.8			0	0.0		39	34.8	
	9-12	1	14.3			0	0.0		11	9.8	
	13-16	1	14.3			0	0.0		4	3.6	
Season	Spring	1	14.3	0.48		0	0.0	-	5	4.5	0.53
	Summer	1	14.3			0	0.0		10	8.9	
	Autumn	5	71.4			1	100.0		81	72.3	
	Winter	0	0.0			0	0.0		16	14.3	
Hematological disease	ALL (male/female)	5 (3/2)	71.4 (60.0/40.0)	0.31		1 (1/0)	100.0 (100.0/0.0)	-	95 (52/43)	84.8 (54.7/45.3)	0.37
	NHL (male/female)	2 (2/0)	28.6 (100.0/0.0)			0 (0/0)	0.0 (0.0/0.0)		17 (17/0)	15.2 (100.0/0.0)	
Clinical symptoms	Bloody diarrhea	7	100.0	>0.99		1	100.0	-	110	98.2	0.87
	Anorexia	6	85.7	0.31		1	100.0		107	95.5	0.34
	Fever	6	85.7	0.35		1	100.0		105	93.7	0.39
	Vomiting	5	71.4	0.54		1	100.0		85	75.9	0.62
	Weight loss	4	57.1	0.43		1	100.0		75	67.0	0.53
	Abdominal cramp	3	42.8	0.47		1	100.0		38	33.9	0.29

two viruses usually cause a lifelong infection in the host, a so-called latent state, which may revert to productive infection under certain conditions, including the weakness of the immune system and other underlying diseases [57]. In the patients under study, EBV was detected in only one male in the ALL group. Most cases of diarrhea caused by EBV

are reported in patients with underlying conditions. Xu et al. (2020) reported that 50.0% of patients with gastrointestinal lesions and a positive EBV result had diarrhea [58]. Sokal et al. (1997) reported clinical signs such as unexplained fever and weight loss, poor appetite, diarrhea, irritability, and EBV-related post-transplant lymphoproliferative diseases among pediatric liver transplant recipients younger than 15 years [59]. Ponticelli and Passerini (2005) also reported gastrointestinal complications caused by various microorganisms including EBV in kidney transplant recipients [60].

According to the results, no CMV-positive cases were observed in this study. CMV is more common among socially disadvantaged groups and geographically poor communities [61]. Since the economic status of the patients was not investigated in this study, it is not possible to give a definite opinion about the cause of most patients' negative results. Except for a few studies that have reported the presence of this virus in subjects with normal immune systems [62, 63], the rest of CMV-positive cases have been reported in people with underlying conditions. Özkale et al. (2015) reported intractable diarrhea caused by CMV colitis in a patient with hematological disease [64]. Dieterich and Rahmin (1991) showed that CMV colitis could be accompanied by non-specific symptoms such as intermittent diarrhea, fever, weight loss, and hematochezia in early stages in HIV-positive patients [65]. Angarone and Ison (2015) also showed that CMV was the cause of diarrhea among solid organ transplant recipients [66].

Interestingly, the positive patients had a history of bloody diarrhea; in addition, the presence of RBCs was reported in their laboratory findings. Since in some reports, bloody diarrhea is one of the exclusion criteria for viral studies [67], the presence of gastrointestinal viruses in this disease may be underreported. However, this clinical manifestation has been reported in some studies. For example, Aminu et al. (2007) in Nigeria reported that 3.0% of adenovirus-positive patients had diarrhea with mucus and blood [68]. In another study, about 10.0% of bloody diarrhea cases were attributed to adenovirus [69]. On the other hand, diarrhea (and in severe cases bloody diarrhea) could be one of the side effects during chemotherapy [70]; therefore, the presence of blood in the stool could not be attributed to viral infection in the patients of this study.

Limitations: Due to budget constraints, we were unable to collect samples newer than those we had. In addition, other pathogens might have caused diarrhea in the studied patients; thus, we do not have data about them at this stage of the project.

Conclusion

This is the first study on the presence of HAdV, EBV, and CMV among children with hematological disorders in this region. The results show that HAdV and EBV are circulating as causes of diarrhea in the studied population, while clinical and laboratory professionals may pay less attention to their role and presence in the development of gastrointestinal diseases. However, diarrhea caused by these viruses is very important in patients and should be considered, especially in immunocompromised patients with negative bacterial cultures. Fortunately, CMV infection was not detected in any of the samples, but monitoring of this virus in the feces of all patients, especially those with immunocompromised conditions, is still important and recommended. Overall, it is recommended to evaluate these viruses in immunocompromised patients with gastrointestinal problems in clinical laboratories.

Additionally, investigation of other viruses as well as bacterial and parasitic pathogens

is recommended for further studies.

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Ethical permissions: The clinical samples collected were in line with the patients' diagnostic stages, and no additional samples were taken. This research complied with the declaration of Helsinki and was approved by the Ethics Committee of Qom University of Medical Sciences (code number: IR.MUQ.REC.1396.89). All actions were performed according to the guidelines and regulations of the committee.

Authors' contributions: HK, SS, AF, and SDMN were involved in supervising the study and writing the manuscript. SS and SDMN were involved in collecting samples, and SY contributed to the project implementation. Also, SS was involved in the analysis of the results. All authors read and approved the final manuscript.

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