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Detection of human adenovirus among Iranian pediatric hospitalized patients suspected of COVID-19: epidemiology and comparison of clinical features

Mohsen Mohammadi[1], Shadi Bid-Hendi[2], Mahnaz Baghershiroodi[3], Mohammad Chehrazi[4], Yousef Yahyapour[5], Azin Gouranourimi[2], Farzin Sadeghi[3]

[1]Non-Communicable Pediatric Research Center, Babol University of Medical Sciences, Babol, Iran;
[2]Student Research Committee, Babol University of Medical Sciences, Babol, Iran;
[3]Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran;
[4]Department of Biostatistics and Epidemiology, School of Public Health, Babol University of Medical Sciences, Babol, Iran;
[5]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

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SUMMARY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children typically results in similar symptoms with other viral respiratory agents including human adenoviruses (HAdVs). Mixed HAdV and SARS-CoV-2 infection (co-infection) in children might result in enhanced or reduced disease severity compared with single infections. The present study aims to investigate the rate of SARS-CoV2 and HAdV infection and also their coinfection and compare the two infections regarding their laboratory and clinical characteristics at hospital admission. A total of 360 combined oropharyngeal and nasopharyngeal swab samples from hospitalized children were examined by real-time PCR for the existence of the SARS-CoV-2 and HAdVs. The symptoms, the clinical characteristics and laboratory findings were retrieved and compared in SARS-CoV-2 and HAdVs positive cases. Of the total 360 suspected COVID-19 hospitalized children, 45 (12.5%) and 19 (5.3%) specimens were PCR-positive for SARS-CoV-2 and HAdV respectively. SARS-CoV-2 and HAdV co-infection was detected in 4 cases (1.1%). Regarding symptoms at hospital admission, fever in SARS-CoV-2 positive group was significantly higher than that in HAdV positive group [34 (85%) vs. 7 (46.7%), p = 0.012]. However, percentages of cases with sore throat, headache, fatigue, lymphadenopathy and conjunctivitis in HAdV positive group were significantly higher than those in SARS-CoV-2 positive group. SARS-CoV-2 and HAdV co-infected children showed mild respiratory symptoms. The present study revealed that SARS-CoV-2 positive children often appear to have a milder clinical course than children with respiratory HAdV infection and children co-infected with SARSCoV-2 and HAdV had less-severe disease on presentation.

Keywords: Severe acute respiratory syndrome coronavirus 2, Human adenovirus, co-infection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus caused an infection surge that has spread quickly throughout the world and was declared a pandemic by the world health organization

Corresponding author
Farzin Sadeghi
E-mail: sadeghifarzin6@gmail.com

(WHO) at the beginning of the 2020. On the onset of the pandemic, few cases of symptomatic COVID-19 had been reported in children worldwide and very few cases have required hospitalization, since children cases spiked dramatically in 2022 during the highly transmissible Omicron variant emergence [1-5]. Compared with adult, the symptoms of SARS-CoV-2 infection in children are mild and pediatric patients rarely develop acute respiratory distress syndrome (ARDS) [3, 6]. Human adenoviruses (HAdVs) play a significant role in pediatric acute respiratory infection, accounting for 5% to 10% of all respiratory tract infections in children including pharyngitis, tonsillitis, pharyngo-conjunctival fever, bronchitis, and pneumonia. In addition, HAdV latent infection in lymphoid tissue has also been described and reactivation with asymptomatic carriage may occur [7, 8]. Recent studies have shown that mixed respiratory viral infection might result in enhanced or reduced disease severity compared with single infections. At the host level, synergistic or antagonistic virus-virus interactions might result in an increased or decreased pathogenesis and good or poor disease outcomes [9]. There is a scarcity of data regarding the comparison of laboratory and clinical characteristics between HAdV and SARS-CoV-2 infection among pediatric patients [10]. In addition, data regarding the clinical characteristics and outcome of mixed HAdV and SARS-CoV-2 infection (co-infection) in children is limited. In the present study, we investigated the rate of SARS-CoV2 and HAdV infection and also their co-infection observed in 360 Iranian children from April 2020 to September 2021 and compared the two infections regarding their laboratory and clinical characteristics at hospital admission.

MATERIAL AND METHODS

Patients and clinical specimens

From April 2020 to September 2021 (period between second and fifth SARS-COV-2 infection surge in Iran), a total of 360 combined oropharyngeal and nasopharyngeal swab samples were collected from hospitalized children suspected to COVID-19 in Amirkola Children's Hospitals affiliated to Babol University of Medical Sciences. The criteria for defining of suspected children COVID-19 cases were according to the Centers for Disease Control and Prevention (CDC). Samples were collected using dry flocked swabs immediately after hospital admission, stored in viral transport medium (Pasteur Institute, Iran) and were shipped with ice to Ayatollah Rohani Hospital laboratory affiliated to Babol University of Medical Sciences. All samples were processed under a class II biosafety cabinet according to standard laboratory biosafety guidelines. After processing, samples were divided into small volume aliquots and frozen at -80°C until the time of examination. Data regarding demographic and clinical features and paraclinical laboratory findings were retrieved from the patients' medical records. None of the enrolled patients in the present study had received COVID-19 vaccine. This study was approved by the Ethical Committee of Babol University of Medical Sciences (ethics code: IR.MUBABOL.REC.1400.032), and written informed consent was obtained from each subject or his/her legal guardian.

Viral nucleic acid extraction

Viral nucleic acid (DNA and RNA) was isolated from 200 µL of swab-storage media using Behperp Viral Nucleic Acid Extraction Kit (BehGene Biotechnology, Shiraz/Fars, Iran) according to the manufacturer's instructions. In brief, for virus particle lysis and purification of viral nucleic acid 200 µL of LB lysis buffer, 25 µL Proteinase K and 6 µL of carrier RNA (2 µg/µL) were added to each 1.5 mL microcentrifuge tube containing swab-storage media. Samples were subsequently incubated at 56°C for 10 minutes until the virus particles were lysed properly. Viral nucleic acid cleanup was performed by mini spin column (silica matrix) according to the manufacturer's instructions.

One step real-time-reverse transcription - PCR for SARS-CoV-2 detection

After viral nucleic acid isolation, samples were immediately subjected to one-step real-time RT-PCR analysis using COVID-19 One-Step RT-PCR Kit (Pishtaz Teb Diagnostic, Iran) according to the manufacturers' protocol (sensitivity =200 copies/mL). Experiments were done in a QIAquant 96 5plex (Qiagen, Hilden, Germany) real-time PCR instrument. The amplification program was adjusted as follow: A) Reverse transcription at 50°C for 15 min, B) cDNA initial denaturation at 95°C for 3 min, C) 45 cycles of denaturation at 95°C for

15 sec and amplification at 55°C for 40 sec. The reporter dye channel sets as 5′ Fluorescein Amidite (FAM) for the viral RNA-dependent RNA polymerase (RdRp) gene; 5′ hexachlorofluorescein (HEX) for the viral Nucleocapsid (N) gene; and 5′ carboxyrhodamine (ROX) for human RNase-P internal control (IC) gene. A cycle threshold (Ct) value of ≤40 was defined as a positive test result.

Detection of human adenoviruses by real-time PCR assay

The presence of HAdV DNA sequences was investigated by qualitative real-time PCR using QIAquant 96 5plex (Qiagen, Hilden, Germany) real-time PCR instrument with the primer sets and TaqMan probe specific for the hexon gene of HAdV as previously described [11]. Each real-time PCR run included reaction mixtures without DNA template as a non-template control (NTC) and plasmid containing cloned target sequences of HAdV hexon gene (Shanghai Gene ray Biotech Co., Ltd) as a positive control. Before testing the clinical samples, the specificity of the real-time PCR technique was evaluated using standard curve analysis using a tenfold dilution series of HAdV hexon plasmid in genomic extracts obtained from HAdV-negative samples.

Statistical analysis

The statistical analyses were performed using SPSS version 22 software (SPSS, Chicago, USA). Statistical differences between groups were assessed by χ^2-test. Normal distribution of the variables was analyzed by the Kolmogorov-Smirnov test. A multiple linear regression model was applied to estimate effects of explanatory variables on quantitative response. *P* value of ≤0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical characteristics

Combined oropharyngeal and nasopharyngeal swab samples were collected from 360 hospitalized children suspected to COVID-19, including 218 (60.6%) males and 142 (39.4%) females (male/female, 1.53/1). Patient age ranged from 1 month to 18 years. The majority of specimens (68.0%) were obtained from children less than 5 years old. No underlying condition or co-morbidity was detected in the vast majority of patients (85.8%). Malignancy (3.1%), congenital heart disease (1.9%), diabetes (1.4%) and kidney disease (1.4%) were the most frequent co-morbidity in the study population. Regarding the severity of respiratory disease, most participants in the present study had mild respiratory disease (95.6%), and severe respiratory disease was observed in 4.4% of children. In the current study no children died during hospitalization.

Detection of SARS-CoV-2 and HAdV

Of the total 360 suspected COVID-19 hospitalized children in our study, 45 (12.5%) patients were PCR-positive for SARS-CoV-2. In SARS-CoV-2 positive group, there were 26 (57.7%) males and 19 (42.3%) females with age ranged from 1 month to 13 years' old. The 45 SARS-CoV-2 positive cases consisted of 27 (14.7%) obtained in 2020 and 18 (10.2%) obtained in 2021. All of 2020 SARS-CoV-2 positive samples were ancestral Wuhan reference strain, however Delta (B.1.617.2) variant was predominant (66.7%) in 2021 positive cases. The mean Ct value in SARS-CoV-2 positive subjects was 29.22±7.63. Regarding SARS-CoV-2 positive cases with co-morbidities only 2 hospitalized children (one case with congenital heart disease and one case with diabetes) were detected in our study.

In total, 19 of 360 (5.3%) specimens were positive for HAdV. In HAdV positive group, there were 8 (42.1%) males and 11 (57.9%) females with age ranged from 1 to 11 years' old. The 19 HAdV positive cases consisted of 8 (42.1%) obtained in 2020 and 11 (57.9%) obtained in 2021. Although HAdV

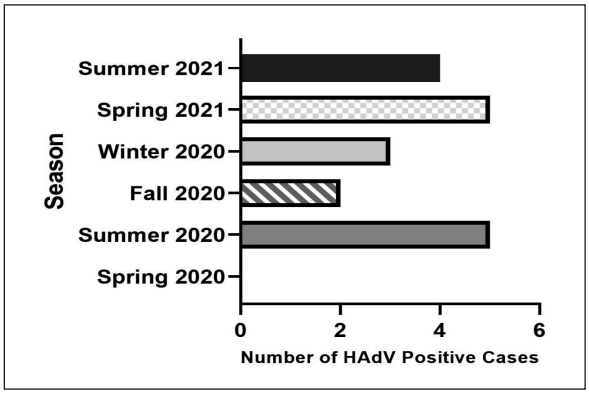

Figure 1 - Seasonal distribution of HAdV infection in suspected COVID-19 hospitalized children from 2020 to 2021.

was detected throughout the year, cases commonly peaked in summer (9 out of 19 positive cases) and spring season (5 out of 19 positive cases) (Figure 1). The mean Ct value in HAdV positive subjects was 31.95±7.15. In terms of HAdV positive cases with co-morbidities only 1 hospitalized child with diabetes was detected in our study.

Clinical features and laboratory findings of SARS-CoV-2 and HAdV infections

Comparison of clinical manifestations and laboratory findings between SARS-CoV-2 and HAdV infected hospitalized children is shown in Table 1. Regarding symptoms at hospital admission, fever in SARS-CoV-2 positive group was significantly higher than that in HAdV positive group [34 (85%) vs 7 (46.7%), p=0.012]. However, percentages of cases with sore throat, headache, fatigue, lymphadenopathy and conjunctivitis in HAdV positive group were significantly higher than those in SARS-CoV-2 positive group (Table 1). In addition, more frequently cough, nasal congestion, shortness of breath, abdominal pain, nausea or vomiting, tremor, and convulsion were reported in the HAdV positive group than in the SARS-CoV-2 positive group, but none of these symptoms showed statistically significant difference between the two groups. Laboratory tests

Table 1 - Comparison of clinical manifestations and laboratory findings between SARS-CoV-2 and HAdV infected hospitalized children.

	Variables	*SARS-CoV2 (N=40)*	*HAdV (N=15)*	*p-Value*
Symptoms and signs	Fever	34 (85%)	7 (46.7%)	0.012
	Cough	19 (47.5%)	8 (53.3%)	0.768
	Shortness of breath	9 (22.5%)	6 (42.9%)	0.175
	Tremor	5 (11.9%)	4 (26.7%)	0.223
	Nasal congestion	9 (21.4%)	7 (46.7%)	0.094
	Sore throat	4 (9.5%)	6 (40%)	0.015
	Headache	3 (7.1%)	5 (33.3%)	0.024
	Fatigue	4 (9.5%)	5 (33.3%)	0.044
	Nausea or vomiting	18 (45%)	6 (40%)	0.771
	Diarrhea	14 (33.3%)	5 (33.3%)	1
	Lymphadenopathy	0 (0%)	5 (33.3%)	0.001
	Conjunctivitis	2 (5%)	5 (33.3%)	0.013
	Convulsion	7 (17.5%)	5 (33.3%)	0.274
	Abdominal pain	3 (7.1%)	4 (26.7%)	0.070
	Co-morbidity	7 (17.5%)	1 (6.7%)	0.310
Laboratory findings	Real-Time PCR Ct Value	29.22 ± 7.63	31.95 ± 7.15	0.186
	WBC ($\times 10^9$/L)	8.35 ± 4.32	11.18 ± 7.10	0.078
	Neutrophil percentage	58.42 ± 20.17	57.86 ± 22.71	0.930
	Lymphocyte percentage	37.79 ± 19.20	37.60 ± 22.78	0.975
	Hemoglobin (g per dL)	11.04 ± 2.69	11.42 ± 1.35	0.602
	Platelet count (µL)	256950 ± 98413	284666 ± 94812	0.352
	CRP (mg/L)	31.73 ± 38.98	31.02 ± 36.92	0.952
	ESR (mm/hr)	21.60 ± 21.74	36.20 ± 33.49	0.066
	Potassium (mmol/L)	4.14 ± 0.52	4.11 ± 0.48	0.804
	Sodium (mmol/L)	132.16 ± 21.30	136.28 ± 4.01	0.463

Note: WBC white blood cell, CRP C-reactive protein, ESR erythrocyte sedimentation rate.

Table 2 - Demographic and laboratory findings of 4 cases with SARS-CoV-2 and HAdV coinfection.

Case	*Age*	*Gender*	*Respiratory Disease severity*	*Adenovirus Real Time PCR Ct*	*SARS-CoV2 Real Time PCR Ct*	*WBC ($\times 10^9$/L)*	*Neutrophil percentage*	*Lymphocyte percentage*	*CRP (mg/L)*	*Potassium (mmol/L)*	*Sodium (mmol/L)*
1	10Y	M	Mild	36	33	8.5	82	7	98	3.92	141.2
2	3Y	F	Mild	35	32	2.5	32	65	71	4.9	140
3	6Y	F	Mild	16	33	11.1	74	20	50	4.0	123
4	1M	M	Mild	19	33	7.3	58	20	1	5.3	136.2

Note: Y years, M male, F female, WBC white blood cell, CRP C-reactive protein.

were done on the day of hospital admission for the hospitalized children. Compared with SARS-CoV-2 positive patients, children with HAdV infection had higher levels of white blood cell (WBC) count and erythrocyte sedimentation rate (ESR), but this difference was not statistically significant (Table 1).

SARS-CoV-2 and HAdV co-infection

SARS-CoV-2 and HAdV co-infection was detected in 4 cases (1.1%). Table 2 shows demographic, clinical and laboratory findings of 4 cases with SARS-CoV-2 and HAdV coinfection. All of the SARS-CoV-2-HAdV co-infected patients had mild respiratory disease. SARS-CoV-2 and HAdV co-infection was not detected in the pediatric patients with co-morbidities.

DISCUSSION

In the current investigation, we evaluated the rate of SARS-CoV2 and HAdV infections in 360 Iranian hospitalized children suspected for COVID-19 from April 2020 to September 2021 and compared the two infections regarding the laboratory, and clinical characteristics at hospital admission. In our study population, HAdV infection rate was 5.3%, which was consistent with previous reports prior and during COVID-19 pandemic [12-15]. Moreover, the positivity rates of HAdV infection did not change significantly during 2020 and 2021 and virus continued to circulate despite the social distancing measures during the COVID-19 pandemic. This may be due to its non-enveloped structure which leaves the virus more resistant to lipid disinfectant and permits its transmission despite mask-wearing [16]. Furthermore, according to several studies, HAdV infection does not show distinct seasonal trends [8, 10, 14-16].

This study was performed by the second through fifth (Delta variant-predominant period) SARS-COV-2 infection surge in Iran. The majority of study population was less than 5 years old and not eligible for COVID-19 vaccination according to Iran's health ministry immunization program. Real-time-reverse transcription-PCR test is considered the reference standard for diagnosis of SARS-CoV-2 infection in symptomatic children. In the present study, SARS-CoV-2 RT-PCR positive rate was 12.5% in hospitalized children suspected to COVID-19. The positivity rates of SARS-CoV-2 RT-PCR vary between 8.6% to 34.1% among suspected children cases in different studies [17-20]. It should be noted that a negative RT-PCR test does not exclude SARS-CoV2 infection specifically in hospitalized children due to poor quality of sampling and late testing or testing in late phases of COVID-19 such as inflammatory phase.

In the present study, SARS-CoV-2 and HAdV co-infection was detected in 1.1% of hospitalized children cases. Co-infection between SARS-CoV-2 and other respiratory pathogens have been reported worldwide, including sporadic cases of HAdV and SARS-CoV-2 infections [15, 21-27]. To the best of our knowledge, there is only one case report study that described adenovirus coinfection with SARS-CoV-2 in a 4-month-old infant, although in some investigations adenovirus and SARS-CoV-2 co-infection has been reported in a low number of adult patients [21, 22, 24, 26-29].

Regarding the clinical characteristics in SARS-CoV-2 positive children our results were consistent with previous research where fever was found to be the most common symptom at hospital admission [18, 19, 30-32]. In agreement with Li et al. research, our results showed that SARS-CoV-2 positive children often appear to have a milder clinical course than children with

respiratory HAdV infection [32]. It is not unusual for HAdV respiratory infection to exhibit sore throat, headache, fatigue, lymphadenopathy and conjunctivitis. These findings are supported by previous studies [7, 33, 34]. Compared with those infected with SARS-CoV-2, we found no statistically significant higher rate of any laboratory findings in those infected with HAdV. In addition, in the current study HAdV and SARS-CoV-2 co-infected children showed mild respiratory symptoms suggesting that viral co-infection had no or limited additional pathogenic role. The current investigation has several limitations. First, it was a single-center study with limited sample size and cases of co-infection was very low, large-scale studies with higher cases of HAdV and SARS-CoV-2 co-infection are needed. Second, our study did not include children who consulted outpatient clinics. Also, our study did not determine HAdV types. The present study demonstrated that HAdV is an important viral infection in hospitalized children suspected to COVID-19. In addition, the current study documented SARS-CoV-2 and HAdV co-infection in hospitalized children.

CONCLUSION

Our results revealed that SARS-CoV-2 positive children often appear to have a milder clinical course than children with respiratory HAdV infection and children co-infected with SARSCoV-2 and HAdV had less-severe disease on presentation. Additional multicenter studies on SARSCoV-2 and HAdV co-infected patients would be welcome to understand the potential viral influence on disease outcome.

Conflict of interest
The authors declare no financial or commercial compete of interest.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards and informed consent was obtained. This project was approved by the Ethics Committee of Babol University of Medical Sciences (Ethics code: IR.MUBABOL.REC.1400.032).

Informed consent
Informed consent was obtained from all individual participants included in the study. Individuals participate this study consent to publish article in a journal.

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