

## Original Article

## Detection of human adenovirus 40/41 among children with some hematological disorders

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### Abstract

**Background:** Different parts of the world are witnessing a significant increase in the prevalence of human adenoviruses (HAdVs) diarrhea among children. This study aimed to assess the prevalence rate of HAdVs type 40 and type 41 (40/41) infections in children with diarrhea and to assess the relationship between viral infection and different socio-demographic and clinical parameters.

**Methods:** A cross-sectional study was recruited to analyze a convenient sample of children presented with diarrhea. Data was collected from 8<sup>th</sup> August 2018 till 6<sup>th</sup> July 2019 at Al-Batool teaching hospital for gynecology and pediatrics in Baquba city, Center of hematology in Baquba city, and the Central teaching hospital of pediatric in Baghdad. Depending on the clinical examination, patients categorized into four groups: Group I with acute diarrhea, Group II with iron deficiency anemia and diarrhea, Group III with thalassemia and diarrhea, and Group IV with leukemia and diarrhea. Each patient gave one stool sample stored in a deep freeze at -20 °C for further analysis. Enzyme-linked immunosorbent assay and immunochromatographic test used to test the samples.

**Results:** A total of 184 children aged one month to fifteen years have been included in this study. More than half (97, 52.7%) of children were males. The prevalence rate of HAdVs 40/41 was 4.34%. Patients in the age group ranged from one month to five years, G IV (leukemia and diarrhea), male gender, low educated mothers, and those who changed to spoon feeder are more likely to have a high prevalence of diarrhea due to HAdVs 40/41. The most top clinical sign was fever (7, 87.5%), and the lowest was the loss weight (1, 12.5%), however vomiting, abdominal pain, and dehydration seen among at least three cases.

**Conclusion:** Human adenovirus 40/41 appeared to play a significant role causing acute gastroenteritis among children with leukemia and less than five years old.

**Keywords:** Gastroenteritis, human adenovirus, immunochromatographic, ELISA, Diyala, Iraq.

### Background

Although it is preventable and treatable, children around the world are increasingly at risk of death due to diarrhea. World Health Organization (WHO) reported that "1.7 billion cases of childhood diarrheal disease every year" [1]. Diarrheal diseases ranked second after pneumonia as the leading cause of death in children and were responsible for more than half-million children deaths under-five age. Anteneh et al. [2] reported that the risk of child mortality due to diarrheal diseases has doubled to "one in nine deaths around the world". Moreover, the high rates of acute diarrhea disease are associated with an economic burden due to an increased number of outpatient visits and days

of hospitalization [3]. Many different agents, including viruses, bacteria, and parasites, can cause acute gastroenteritis [4]. Among the significant causative viral agents of acute gastroenteritis are rotaviruses, caliciviruses, norovirus, and human adenovirus (HAdVs) [5]. Diarrhea infections caused by the enteric serotypes of human adenovirus (HAdVs) are common among children, especially infants. Enteric adenoviruses characterized by its ability to settle in the intestines and spread by ingestion of the contaminated food and drink. Most of the clinical signs, such as "low-grade fever, vomiting, abdominal pains, and dehydration," appear after an incubation period of one week to ten days [6]. The prevalence of morbidity and mortality tends to increase among the patients of hematological malignancies such as B-cell lymphoma and multiple myeloma when they exposed to viral infection [7]. Renzi et al. [8] reported that young children presented with acute myeloid leukemia (AML) are prone to fatal bacterial and

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fungal infections; however, the role of adenovirus infection has not been discussed extensively in the literature.

In the Iraqi file, since the US-led invasion in 2003 the infrastructure has been destroyed, including health institutions. The successive waves of internal conflicts have led to the displacement of several million people. The health situation was very deteriorated because of administrative corruption and lack of seriousness in providing strategic solutions [9].

World Health Organization, in its report for the December 2017, reported that about 17692 new cases of acute diarrhea in Iraq. Acute diarrhea was in the tip of diseases all over Iraq in 2017 [10]. Several investigations have been undertaken to elucidate the role of enteric adenoviruses among children in different places of Iraq [11-25]. Two studies from north of Iraq reported that the prevalence of adenovirus among children was 4.0% and 13.2% in Sulaimani province and Zakho city respectively [11,12]. A study conducted in Baghdad found that the prevalence of adenovirus is 6.0% among children less than five [13]; however, Al-Sadawi et al. [14] indicated that the prevalence was high (34.4%) in Al-Najafi province. This study aimed to assess the prevalence rate of human adenovirus (HAdVs) type 40 and type 41 infections and the relationship between the viral infection and different socio-demographic and clinical parameters among a sample of children under five years of age presented with diarrhea in the province of Diyala, Iraq.

## Methods

### Study sample

A cross-sectional study was conducted from 8th August 2018 till 6th July 2019 among children presented with diarrhea. Data was collected from Al-Batool teaching hospital for gynecology & pediatrics in Baquba city, Center of hematology in Baquba city, and the Central teaching hospital of pediatric in Baghdad.

### Study tool

A convenience sample was collected using a semi-structured questionnaire. A well trained team was used to interview the parents of children after explaining the objective of the study and giving the oral consent. All children aged one month to fifteen years old, presented with acute diarrhea, and willing to participate were included, however the parents who are not willing to participate, children more than fifteen years or less than one month age and the severely ill children were excluded from the study.

### Study procedures

At the time of the study, depending on the clinical examination and the laboratory findings, 184 children are included and categorized as follows: Group A- Consist of 46 children with acute diarrhea. In this group, children presented with sudden onset of loose or watery diarrhea (three times or more per day) and lasting seven days but not more than two weeks [26]. Group B- Consist of 46 iron deficiency anemia patients with diarrhea. The diagnosis of anemia performed by complete blood count (CBC) test including the differentials to look for microcytic or macrocytic anemia and hypochromic or normochromic anemia. Moreover, the iron studies used to test for serum iron, iron-binding capacity, serum ferritin and transferrin levels [27]. Group C: Consist of 46 thalassemic

patients with diarrhea. In this group, the protein-based technique, such as electrophoresis and chromatography were necessary to diagnose the patients with thalassemia [28]. Group D: Consist of 46 children presented with leukemia and diarrhea. Both complete blood count and bone marrow aspiration used to diagnose an excess of abnormal white blood cells (leukocytosis) as a common finding with the leukemia disease [29].

### Laboratory analysis

The enzyme-linked immunosorbent assay and the immunochromatographic test was used to determine HAdVs 40/41. Approximately 1.0 ml of stool sample was collected from each patient. The samples were kept in an Eppendorf tube and stored in a deep freeze at -20°C.

### Statistical analysis

The statistical package for social sciences (SPSS) was recruited to analyze the data. All categorical variables were expressed as frequency and percentage.

## Results

### Deceptive analysis

The surveyed children were in the age range of 1 month to 15 years. More than half (97, 52.7%) of children were male compared to 87 (47.3%) were females. Out of 184 children presented with acute diarrhea, 8 cases (4.34%) were positive for HAdVs 40/41 using an enzyme-linked immunosorbent assay, and one step colored chromatographic immunoassay, Figure (1).

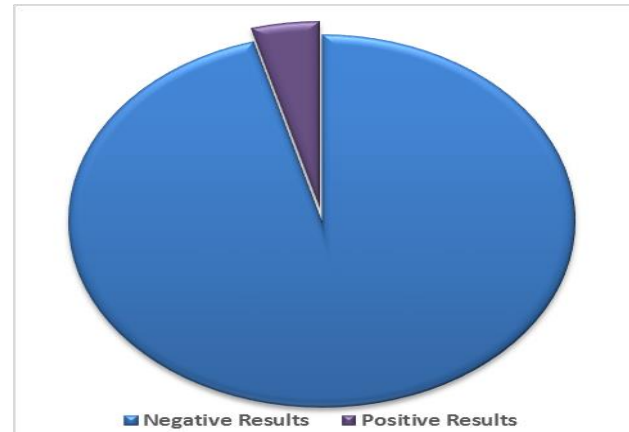


Figure 1: Distribution of human adenovirus 40/41 in the studied sample

HAdVs 40/41 gastrointestinal induced infection was noticed in five males (62.5%) compared to three females 3 (37.5 %). In most of the cases, 7 (87.5%) appeared among the age group of one month to five years. Group VI appeared to have more cases than other groups. Moreover, the highest percent (6, 75.0%) of cases were belonging to mothers with primary education compared to two cases (25%) with higher education. The highest infection rate was noticed among the patients who used fed table food 4 (50%), and three cases (37.5%) appeared among those who were used artificial feeding formula. Although the sources of drinking water were the tape water (3 cases) and filter water (3 cases), however, 2 cases claimed that they use boiling water (Table 1).

The baseline clinical manifestation of the study population was detailed in Table (2). Out of eight positive cases, seven (87.5%) children presented with high-grade fever. Vomiting, abdominal pain, and dehydration appeared in three cases for each (37.5%). One case had weight loss (12.5%).

## Discussion

In this study, the prevalence rate of HAdVs 40/41 was 4.34%, which was consistent with the findings of some local and international studies [12,15]. Mero et al. [12] and Yassin et al. [15] found that 4.0 % and 4.6% of pediatric patients presented with diarrhea in Zakho city and Baghdad city. Similar findings (5.1%) reported by Najafi et al. [30] in south of the Iran, and Renzi et al. [8] study among Canadian children with adenovirus infection in acute myeloid Leukemia (AML). These rates of HAdVs 40/41 disease could be associated with the same social habits of the population, sample size, patient age, duration of the study, and laboratory method used in the examination. The prevalence rate of HAdVs 40/41 in our study was higher compared with other studies done in Iraq [11,16]. Jaff et al. [11] found that the rate of human adenovirus in Sulaimani province was 2.0%, and Al-Sayidi et al. [16] recorded 2.6 % in Baghdad, respectively. Moreover, in this study the prevalence rate of

HAdVs 40/41 was higher than the prevalence rate (2.3%) reported by Hamkar et al. [31] and (3.5%) reported by Moyo et al. [32] among diarrheic children in Northern Iran and Tanzania, respectively. Several factors may lead to different rates of infection, such as the geographical regions and the social habits of the population, e.g., personal hygiene. The environmental variations, using fresh or frozen stool specimens in the collection of samples, laboratory techniques used, such as using different kits for the same method, are various factors that have a direct effect on the results of the study. Furthermore, the study focused on the pediatric age group, where the morbidity risk is high and more susceptible to opportunistic infections, either bacterial or viral, than other age groups. Furthermore, the prevalence rate of HAdVs 40/41 was lower than other studies done in and outside Iraq [17,18]. Zaman et al. [17] and Al-Khafaji and Al-Mola [18] recorded adenovirus rates at 6.0% and 16.4% among hospitalized patients from Tikrit and Babel provinces, respectively. Considering the international literature, Sharifi-Rad et al. [33] and Ozsari et al. [34] found that rate of HAdVs 40/41 was 20.3% among children admitted to internal laboratory and central laboratory of Zabol in Iran and 26.2% in pediatric patients admitted to the hospital Igdır province Turkey respectively.

**Table 1** Demographic characteristic among studied groups (n=184).

Variable Factors		Diarrhea Group		ID Anemia Group		Thalassemia Group		Leukemia Group	
Gender type	Male	24(52%)	+	27(59%)	+	24 (52%)	+	22(48%)	++
	Female	22 (48%)		19(41%)		22 (48%)		24(52%)	+++
Age groups	1 m-5 y	45 (98%)	+	41(89%)	+	25 (54%)	+	20(43%)	++++
	6-10 years	1(2%)		4 (9%)		11(24%)		19(41%)	+
	11-15 years	0		1(2%)		10(22%)		7 (15%)	
Mothers education	Illiterate	11(24%)		7(15%)		2 (4%)		4(9%)	
	Primary	13(28%)	+	14(30%)	+	21(46%)	+	8(17%)	+++
	Secondary	3(6%)		13(28%)		5(11%)		20 (44%)	
	Higher education	19(42%)		12(26%)		18(39%)		26(56%)	++
Type of feeding	Breast	9(20%)		12(26%)		2 (4%)		1 (2%)	
	Artificial	20(43%)		20(43%)	+	8(17%)		2(4%)	++
	Mixed	7(15%)	+	9(20%)		1 (2%)		4(9%)	
	Table food	10(22%)		5 (11%)		35 (77%)	+	39(85%)	+++
Sources of Water	Tape water	13(28%)	+	11(24%)		9(20%)		17(37%)	++
	Boiled	3(7%)		5(11%)		11(24%)		7(15%)	++
	Filter water	30(65%)		30(65%)	+	26(56%)	+	22(48%)	+

**Table 2** Clinical manifestation among studied groups (n=184).

Clinical manifestation		Diarrhea No. (%)	ID Anemia No. (%)	Thalassemia No. (%)	Leukemia No. (%)
Fever	Yes	28(61%)	27 (59%)	19(41%)	37(80%)
	No	18(39%)	19(41%)	27(59%)	9 (20%)
Vomiting	Yes	37(80%)	35 (76%)	5(11%)	16 (35%)
	No	9(20%)	11 (24%)	41(89%)	30(65%)
Abdominal pain	Yes	12(26%)	10(22%)	11(24%)	11(24%)
	No	34(74%)	36 (78%)	35(76%)	35(76%)
Weight loss	Yes	11(24%)	15(33%)	7(15%)	15(33%)
	No	35(76%)	31 (67%)	39(85%)	31(67%)
Dehydration	Yes	29(63%)	30 (65%)	9 (20%)	12(26%)
	No	17(37%)	16 (35%)	37(80%)	34(74%)

ID: Iron deficiency anemia, +: Positive case for human adenovirus 40/41

The high frequency of the disease could be related to the insufficient knowledge of families about the disease and the ease of other individuals becoming infected due to inadequate hygiene conditions, poor access to hydration therapy, and the higher prevalence of undernourishment children. In part of our results, four cases within the leukemia group were positive for human adenovirus. Indeed, the human body uses the hematopoietic system to keep "the number of cell births and deaths equals within each time unit in what is call the basic hematopoietic law." However, in some cases, such as acute leukemia, an abnormal maturation, and dysregulated proliferation of leukocytes replace the normal hematopoiesis process [35]. Almand et al. [29] pointed that abnormal hematopoiesis coupled with significant bone marrow infiltration leads to a deterioration in the production of normal granulocytes, and the outcome will be emerging neutropenia with impaired function of granulocyte [36]. Prolonged neutropenia is often related to increasing in the severity of illnesses [37]. There was no difference between the two laboratory methods used in this study. Leclipteux et al. (1998) showed that both ICT and ELISA had the same specificity and sensitivity [37]. However, Kim et al. [39] compared between ICA, ELISA and real-time PCR for the detection of adenovirus in clinical stool specimens and found (7.5%) (6.3%) (10.3%) for each one respectively. Al-Khafaji and Al-Mola [18] recorded rapid test (16.4) and 2 (0.8) by ELISA test for HAdVs 40/41 detection [18].

Regarding the sociodemographic factors, when comparing the gender, this study found that the frequency of human adenovirus 40/41 infection was higher in male patients (5, 62.5%) compared to females (3, 37.5%). Similar findings seen in earlier studies conducted in Iraq, such as the study done by Mero et al. [12] in Zakho city, north of Iraq [12], Al-Sadawi et al. [14], in Al-Najaf Province in the south of Iraq [14] and Khoshnaw [20] in Erbil Province. The high rate of HAdVs 40/41 infection among children in the male gender may be related to the fact that males are more involved with outdoor activities than their counterparts. The males are more active, mobile, and integrated into the environment, especially among agricultural communities, compared to females who are more likely to prefer to stay at home and eat home-cooked food. Moreover, females have a lower risk of microbial inflammatory infections than males because of "the prolonged humoral and cell-mediated immune responses" [40]. However, Savadkoohi et al. [41] showed that the rate of HAdVs 40/41 among Iranian female children was significantly higher than in males. Al-khafaji and Al-Mola [18] found that the rate of HAdVs 40/41 was similar among girls and boys from Hilla city in Iraq.

Findings of this study found that HAdVs 40/41 infection was higher among age group less than five years compared to the older children, which correspond to some other studies conducted earlier in different regions of Iraq such as Baghdad province [13], Erbil Province [20], and Thi-Qar province [21]. Children less than five years are more susceptible to diarrheal disease than the older age groups, because of diminish of immunity. The number of tranche-placental antibodies of the child starts dwindling after six months of age. Moreover, children in the age of creeping are more likely to catch viruses mixed with the patient's vomiting. [19].

In this study, we found that the rate of HAdVs 40/41 infection was higher among mothers with primary education. A similar finding was reported in Tanzania [32]; however, Alaa et al. [22] recorded that the rate of adenovirus was higher among the educated compared to low educated mothers in Baghdad. Several factors may participate in raising the frequency of adenovirus infection among the low-educated families, such as the nutritional and food consumption of children and the family. Females with limited education are less likely to adhere to proper cooking and handling of food. On the other hand, educated women are expected to be keener on boiling drinking water for children and thus less exposure to pathogens. Findings from earlier local studies in Sulaimani province [11] and Al-Najaf province [23] support our results that children who depend on breastfeeding or mixed were less likely to be infected than those who rely on the artificial and table feeding. Mothers often resort to feeding children using the bottle instead of breastfeeding when they suffer from malnutrition, chronic disease or because of breast disease. It is well known that artificial feeding is one of the most important sources of infection for infants, for example preparing milk under unsanitary conditions, using contaminated water, or bottle nipple contamination. Moreover, the dependence of children on artificial feeding often ends with malnutrition and a weak immune system, which predisposes to an increased risk of disease. Literature proved the role of breastfeeding in the protection against acute and chronic diarrheal infection [42]. The surveyed patients indicated the use of tap water in three positive cases of HAdVs 40/41 infection. Similar result was reported in Thi-Qar province, Iraq [21].

In fact, the infrastructure facilities and services are very deteriorated in Iraq since 2003. The constant cuts of electric power and the lack of safe drinking water prompted many people to use river water directly without boiling or sterilization. In addition, intermittent water supply has forced people to store water in an invalid reservoirs (tanks) for a long time. The chloride concentration is often insufficient to disinfect water, which may be contaminated with underground sewage. However, Jaff et al. [11] in his study Sulaimani Province showed that rate of HAdVs 40/41 was higher among people who used the sterilized water than those who used the piped water. Jaff et al. [11] explained that the reason for that is the sample of study which was collected from around Sulaimania city, and respondents were mostly from urban and semi-urban districts where the qualities of water supply are better than elsewhere [11].

Different type of clinical feature was studied in this study. Fever was reported in 7 cases (87.5%) out of the 8 positive cases in this study. Three cases reported for each of the vomiting, abdominal pain, dehydration. Weight loss was reported for one case. The clinical features of our patients are like those previously described by the study done in Hilla Province [18] in Baghdad city [15]. Moreover, Yassin et al. [15] in Baghdad found that most of the children with acute diarrhea developed fever, yet those positive to HAdVs 40/41 developed fever more significantly (90.7%) than those without HAdVs 40/41 (74.6%). However, two studies from Iran [31] and the United States [43] had found no fever in patients with enteric adenovirus infections. The result of the present study found that three cases (37.5%) each had a vomiting, abdominal pain and

dehydration. Similarly, Afrad et al, (2018) [44] in Bangladesh, indicated that the highest rate of clinical feature associated with adenovirus infection were vomiting, abdominal pain, dehydration, and fever. Al-Ameed et al. (2015) in the Najaf province of Iraq found that most clinical features in infants were abdominal pain, vomiting, and high fever [24].

This study demonstrates one case out of 8 cases (12.5%) was suffering from weakness, which is unlike result of Al-Dahmoshi et al. [45] in Babylon Province [45], where the clinical features of infants with viral diarrheal infections included weakness, fever > 38°C, abdominal pain and vomiting [46]. The similarity in the clinical feature due to the nature of areas, close geographical conditions which might be a factor for this similarity in adenoviral trend timing. But variations could be explained by the duration of the study, patients' age, number of samples. Moreover, the high incidence of diarrhea confirms the need for effective early diagnosis programs among children such as the Integrated Management of Neonatal and Childhood Illness (IMNCI) in the primary health care (PHC) [46].

This study complaints from some determinations; first, data was collected from only two centers, this may hinder its generalization at the national level, yet it reinforces other results achieved in Iraq. Second, in the cross-sectional design hard to build a causal relationship among the variables. Third, this study may complaint of bias collection because of convivence sampling technique.

## Conclusion

The prevalence rate of HAdVs 40/41 was 4.34% among four different groups of children aged one month to fifteen years. Depending on the clinical examination, patients categorized into four groups: Group I with acute diarrhea, Group II with iron deficiency anemia and diarrhea, Group III with thalassemia and diarrhea, and Group IV with leukemia and diarrhea. Infection with human adenovirus 40/41 significantly causing acute gastroenteritis among children with leukemia and those aged less than five years old. The impact of immunity among females was apparent, males were more likely to have viral infections than their counterpart. Moreover, viral infections increase as maternal education decreases. Social habits and diet of the family have a significant impact on the emergence of viral infections. The more the child away from breastfeeding and approached the use of spoon feeder, the higher the incidence of viral infections. Providing safe water and attention to hygiene reduces the incidence of viruses among children.

## Abbreviations

ELISA: enzyme linked immunosorbent assay, AIDS: acquired immune deficiency syndrome, WHO: World Health Organization, ADD: Acute diarrheal disease, HAdVs: human adenovirus, AML: acute myeloid leukemia.

## Declarations

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## Availability of data and materials

Data will be available by emailing areej.2002@yahoo.com

## Authors' contributions

AAH and NSM are responsible for designed the study and coordinated all aspects of the research including all steps of work. AYA is responsible for the sample collection and processing. AYA, AAH and NSM are writing, reviewing, editing, and approving the manuscript in its final shape.

## Ethics approval and consent to participate

The study design was approved by the Ethical Committee at College of Medicine, University of Diyala (Approval Number: MD29 June 2018 AYA).

## Consent for publication

Not applicable

## Competing interest

The authors declare that they have no competing interests.

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