Adenovirus Infections in Jordanian Hospitalized Pediatric Patients: Prevalence and Clinical Features

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Abstract

Background and aims: Adenovirus is an important cause of respiratory infections in infants and children. Information on the prevalence, seasonal distribution of adenovirus and the clinical symptoms associated with it is not available in Jordan. Therefore, this study was conducted on 200 hospitalized children less than 2 years of age.

Methods: Hep-2 cells were inoculated with nasopharyngeal aspirates (n = 200) and adenovirus antigens were detected by cell culture technique. The monthly distribution of the adenovirus isolates in relation to the climatic factors was determined. The associated clinical characteristics were also investigated.

Results: Adenovirus infections were documented in 11.5% of patients, peaked in the 7-9 months age group and manifested mainly as bronchopneumonia. Fever (> 380C rectal) was observed in 74% of adenovirus-infected patients. There was no significant differences between the hospitalized adenovirus-infected and adenovirus-negative patients with respect to hypoxemia, tachypnea, retractions, crackles, hyperinflation, interstitial infiltration and consolidation. Abnormal chest X-ray with interstitial infiltrates was significantly ($p < 0.05$) more associated with adenovirus negative patients.

Adenovirus infection is characterized by autumn-early winter seasonal pattern. The adenovirus infections began in September peaked in December and disappeared in spring and summer. This distribution was not significantly correlated with temperature, rainfall and relative humidity.

Conclusion: The epidemiology of adenovirus could help in considering it in diagnosis of children between September and December each year, and planning of prevention and control programs in Jordan.

Keywords: Adenovirus, epidemiology, clinical features, Jordan.

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Introduction

Adenovirus is a well-known causative agent of pediatric Upper and Lower Respiratory Tract Infections (LRTIs). It is the second most common viral pathogen in children under two years of age [1, 2] and accounts for 10% of LRTIs in hospitalized children under the age of 4 years. [3-6]

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Most adenovirus LRTIs are mild and some are severe that can result in fatal outcome or residual sequelae. [7-8]

The prevalence of adenovirus has been reported for Western, [5, 9-10] Asian, [4, 11,12] and some Middle East countries. [13-15] It represents 0.8-27.3% of viral respiratory infections in these countries. Adenovirus infections occur endemically throughout the year in some countries, [5, 7, 11, 13] while in others it occurs epidemically and predominates during spring [16] or winter. [2, 4, 6, 10, 17]

A previous study conducted on pediatric patients in the north of Jordan reported that the prevalence of adenovirus was 15.4%. [14] The seasonality of this virus and the clinical features associated with it were not described in this study. Therefore, the aim of the present study was to conduct an in-depth investigation of all these parameters together in hospitalized children who were screened previously for the respiratory syncytial virus, [18] in order to provide useful insights into the epidemiology of adenovirus in Jordan; which could be helpful to clinicians and researchers interested in the control of viral respiratory tract infections.

Methods

Patients: The study population included all hospitalized children (n=200) less than 2 years of age who were admitted with clinical evidence of respiratory illness between September 2002 and March 2004 to the pediatrics department of the Islamic hospital in Amman, capital of Jordan. This hospital is a major referral hospital in Jordan with about 4000 admissions each year to the pediatrics department.

In Jordan, adenovirus detection is not routine in hospitals and, therefore, the study was approved by hospital's ethics committee and the parents of patients who signed the consent form.

Clinical characteristics: Clinical characteristics of enrolled patients were obtained from their profiles in Islamic hospital.

The clinical characteristics of adenovirus-positive patients were compared with the clinical characteristics of adenovirus-negative patients in the study population. The association of the clinical characteristics of adenovirus-positive patients with breast feeding, antibiotic usage, otitis media, and smoking in the household was also investigated.

Specimens, virus isolation and immuuofluorescence analysis: Nasopharyngeal aspirates (n = 200) were obtained from children at the Islamic hospital and were transported immediately on wet ice to the Virology Research Laboratory at the University of Jordan for inoculation into Hep-2 cells. The inoculated cells were incubated for 10 days for the characteristic cytopathic effect. Cells were then spotted into a well (6-mm diameter) of eight-well Teflon-coated microscope slides (ICNI, USA). Two slides of infected cells were prepared. One slide was used for screening of respiratory viruses which can be grown in Hep-2 cells using the commercially available Imagen Respiratory Screen Kit (Dako, Denmark). Those viruses include the respiratory syncytial virus detected in a previous study in the same population [18] and adenovirus (present study). If either well in the screening slide gave a positive result, the corresponding well in the second slide was used to detect adenovirus by the direct immunofluorescence technique according to the manufacturer's recommendation using the Imagen Adenovirus Kit (Dako, Denmark).

Weather data: Weather data (mean monthly temperature, humidity, and total monthly rainfall) were obtained from the meteorological department of Jordan in order to determine the seasonal distribution of adenovirus in Jordan.

Statistical analysis of data: The prevalence of adenovirus in the clinical specimens was determined by the true probability. *P* values calculated under the one-tailed normal distribution were used to determine the dependency of the clinical factors on the prevalence of adenovirus, and $p < 0.05$ was considered statistically significant.

The relationship between the prevalence of adenovirus and the climatic conditions was tested by calculation of the correlation coefficient (r). [19]

Results

1. Adenovirus

1.1. Prevalence of adenovirus

The prevalence of adenovirus during the studied period is shown in Figure (1). Adenovirus accounted for 11.5% (23/200) of the studied cases with a confidence interval of 0.07-0.16. Adenovirus accounted for 26.5% (18/68), 5.2% (5/97) and 0% (0/35) of the cases admitted and tested in 2002, 2003, and 2004, respectively. Adenovirus-negative specimens accounted for 73.5% (50/68), 94.8% (92/97) and 100% (35/35) of the total specimens screened in 2002, 2003 and 2004, respectively.

1.2. Seasonal distribution of adenovirus

The monthly distribution of adenovirus isolates in relation to the climatic factors is shown in Figure (2). The distribution of adenovirus did not show a significant correlation with mean temperature (r = -0.209), mean rainfall (r=0.255) or mean relative humidity (r= 0.374). Adenovirus infection is characterized by autumn-early winter seasonal pattern. In autumn, adenovirus infections began in September 2002 and September 2003 when the monthly mean temperature was 24.7°C and 23.6°C, respectively. In these months, the total rainfall was 0 mm and the mean monthly relative humidity was 54.9% and 52%, respectively. In early winter, the occurrence of adenovirus peaked, especially in December 2002 and 2003, when the monthly mean temperature was 9.9°C and 9.4°C, respectively, the total rainfall was 93.8 mm and 72 mm, respectively and the mean monthly relative humidity was 84.9% and 79.6%, respectively. Adenovirus infections disappeared with the end of December of each year. Adenovirus does not circulate in spring and summer.

2. Patients

2.1. Sex and age of patients

Males were more commonly affected by adenovirus than females ($p< 0.05$), and the male-to-female ratio was 1.9:1 (Table 1). The occurrence of adenovirus infection in the first year of life (78.3%) was significantly ($p< 0.05$) higher than that in the second year of life (21.7%) and peaked in the 7-9 months age group (30.4%).

2.2. Clinical characteristics of Adenovirus infection

The syndromes and clinical characteristics of the enrolled patients on admission are shown in Table (2). Twenty one percent and 56.5% of adenovirus-infected patients had bronchiolitis and bronchopneumonia, respectively. Fever (> 38^0C rectal) was noted in 74% of adenovirus-infected patients, and there was no significant difference ($p > 0.05$) between them and the adenovirus-negative patients (71.8%). Adenovirus-infected infants who were more than three months of age (94%) were more likely to be febrile than younger infants (6%).

There was no significant difference ($p>0.05$) between adenovirus-infected and negative patients with respect to hypoxemia, tachypnea, retractions, crackles (Table 2). Abnormal chest X–ray with interstitial infiltrates was significantly ($p< 0.05$) more associated with adenovirus-negative patients.

The average stay of adenovirus-infected patients in the hospital was three days with no admission to ICU or mortality. After admission, antibiotics were administrated to 95% of the adenovirus-infected infants and to 84.7% of negative infants (Table 2). Thirty five percent of adenovirus-infected infants developed otitis media compared to 14.1% of the negative patients and there was a significant difference ($p<0.05$) between the two groups. There was no significant difference ($p > 0.05$) between adenovirus-infected infants and negative patients with respect to the breastfeed and smoking in the household (Table 2).

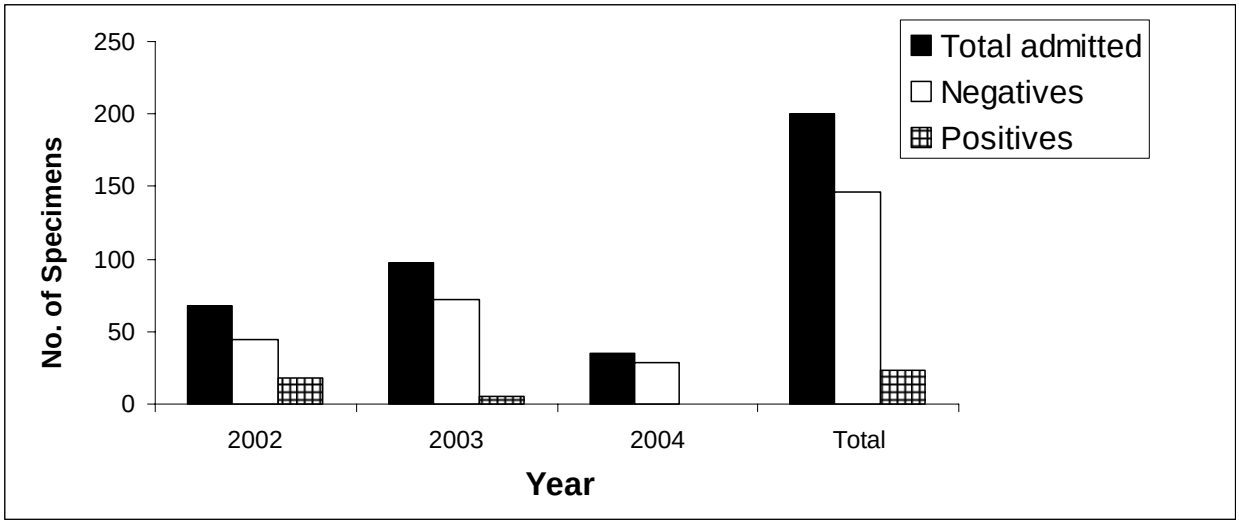

Figure (1): Total number of admitted and tested patients, adenovirus negative and adenovirus positive patients.

	2002				2003												2004			
	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	
Number of admitted Patients	10	18	12	28	18	20	21	0	0	0	0	0	9	11	7	11	17	10	8	200
Ad Negative Patients	8	15	7	15	13	12	18	0	0	0	0	0	8	10	7	6	10	9	8	146
Ad Positive Patients	2	3	5	8	0	0	0	0	0	0	0	0	1	1	0	3	0	0	0	23

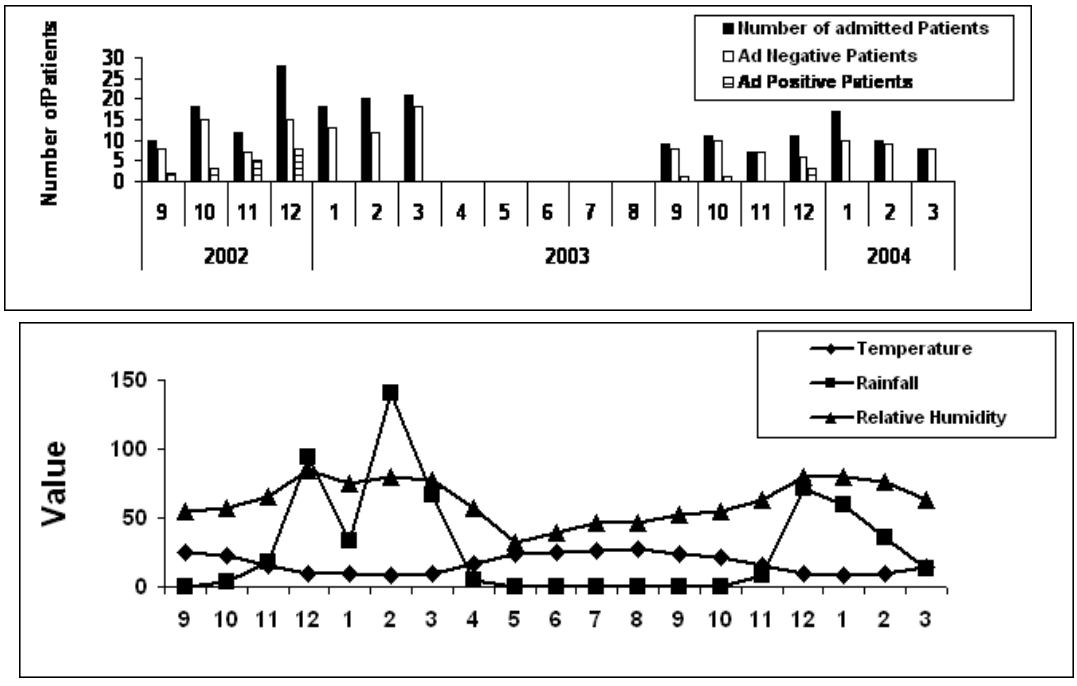

Figure (2): Monthly number of admitted, adenovirus positive and negative patients in relation to mean temperature (ºC), rainfall (mm) and relative humidity (%).

Table (1): The demographic characteristic of adenovirus-infected children.

Characteristics	*Total No. (%) of patients*	*No. (%) of adenovirus-infected patients*
Males (M)	*113 (56.6)*	*15 (65)*
Females (F)	*87 (43.5)*	*8 (35)*
M:F ratio	*1.3:1*	*1.9:1*
Age groups (Months):		
First Year of Age		
[1-3]	*46 (23)*	*2 (8.7)*
[4-6]	*38 (19)*	*6 (26.1)*
[7-9]	*34 (17)*	*7 (30.4)*
[10-12]	*29 (14.5)*	*3 (13)*
Total	*147 (73.5)*	*18 (78.3)*
Second Year of Age		
[13-18]	*26 (13)*	*3 (13)*
[19-24]	*27 (13.5)*	*2 (8.7)*
Total	*53 (26.5)*	*5 (21.7)*

Table (2): The syndromes and clinical characteristics of the enrolled patients on admission.

Characteristics	*Ad-positive n= 23*		*Negative* n=177*		*Total n=200*		*P values°*
	No.	*%*	*No.*	*%*	*No.*	*%*	
Bronchiolitis	*5*	*21.7*	*56*	*31.6*	*61*	*30.5*	*0.3378*
Bronchopneumonia	*13*	*56.5*	*67*	*37.9*	*80*	*39.5*	*0.0894*
fever (≥ 38 C°, axillary)	*17*	*74*	*127*	*71.8*	*144*	*72*	*0.8301*
infants aged ≤ 3 months	*1*	*6*	*25*	*14.1*	*26*	*18*	*0.195*
infants aged > 3 months	*16*	*94*	*102*	*57.6*	*118*	*82*	*0.2793*
Hypoxemia O2 sat<95%	*5*	*22*	*58*	*32.8*	*63*	*31.5*	*0.2899*
Tachypnea (≥50/min)	*5*	*22*	*70*	*39.5*	*75*	*37.5*	*0.1011*
Retractions	*5*	*22*	*60*	*33.9*	*65*	*32.5*	*0.2472*
Crackles	*17*	*74*	*123*	*69.5*	*140*	*70*	*0.6671*
Chest X-ray findings:							
Abnormal	*12*	*52*	*143*	*80.8*	*155*	*77.5*	*0.0023*
Hyperinflation	*3*	*13*	*36*	*20.3*	*39*	*19.5*	*0.4118*
Interstitial infiltrates	*6*	*26*	*89*	*50.3*	*95*	*47.5*	*0.0308*
Consolidation	*3*	*13*	*18*	*10.2*	*21*	*10.5*	*0.676*
Received antibiotics	*22*	*95*	*150*	*84.7*	*172*	*86*	*0.1612*
Associated Otitis Media	*8*	*35*	*25*	*14.1*	*34*	*17*	*0.0131*
Breast feeding	*16*	*70*	*130*	*73.4*	*146*	*73*	*0.6968*
Smoking in household	*14*	*61*	*135*	*76.3*	*149*	*74.5*	*0.1152*

Ad: Adenovirus

****Negative: Specimens showed negative result using the Imagen Adenovirus Test Kit.***

°P values for differences between Ad-positive and negative patients.

Discussion

Adenovirus is an important cause of respiratory infections in infants and children. In the present study, adenovirus accounted for 11.5% of the total admitted and tested patients and expected with 95% confidence to find adenovirus infection in 7-16% of the respiratory cases. The prevalence of adenovirus in Amman was almost similar to its prevalence (15.4%) in Irbid, north of Jordan [14] and within the range (0.8-27.3%) reported in other countries. [2, 4, 10, 11, 13, 16, 17]

Adenovirus caused infections in autumn and early winter, peaking in December of 2002 and 2003, which could be explained by staying indoors in cold rainy weather and droplet transmission of adenovirus within confined spaces. In contrast, other studies reported the distribution of adenovirus throughout the year without epidemics [5, 7, 11, 13] or with epidemics during spring [16] or winter. [2, 4, 10,17]

Males were more affected than female hospitalized patients, which agrees with reports from other countries. [4, 7, 11] Adenovirus infections peaked in the 7-9 months age group (30.4%) (Table 1) which is in agreement with other reports. [20] Infants of < 6 months of age are normally protected by maternal antibody to adenovirus. This reduces the severity of infections and the requirement for intensive care unit admission and mechanical ventilation. [7]

Adenovirus in the hospitalized patients was associated mainly with bronchopneumonia (Table 2) which is consistent with other reports. [4, 11]

It is known that adenoviral viremia is common, [8,21] and high and prolonged fever is frequently associated with adenovirus infections in hospitalized children. [7] Seventy-four percent of our patients experienced fever (Table 2) and this frequency is similar to that reported by other investigators. [9] The high fever associated with adenovirus infections does not differ significantly from fever in severe bacterial infections. [21] Therefore, unidentified aetiological agents including bacteria or other respiratory viruses may contribute to fever observed in 71.8% of our negative patients.

There was no significant difference between hospitalized adenovirus-infected and negative patients with respect to hypoxemia, tachypnea, retractions and crackles. On the other hand, hyperinflation, interstitial infiltration and consolidation were significantly more associated with adenovirus negative patients (Table 2). This could be explained by mild adenovirus infection since there was no mortality or need for ventilators, or ICU admission. In contrast, other investigators [7] reported higher percentage of hyperinflation (54%) and consolidation (82%) in patients with severe adenovirus lower respiratory tract infection. Also, others [8] reported that chest retraction was significantly more common in the adenovirus pneumonia patients.

In the present study, 95% of the hospitalized adenovirus-infected patients were given antibiotics. This extensive use of antibiotics (i) is due to the unavailability of the diagnostic virology laboratories in Jordan which results in administration of antibiotics to all respiratory infected patients, and (ii) resulted in lower rate (35%) of otitis media (Table 2) compared to 55%-70% in other countries. [22] One of the reasons behind the usefulness of this study is to provide a basis to avoid inappropriate antibiotic therapy for adenovirus infections in the light of unavailability of adenovirus diagnostic tests. Therefore, if the clinician considers the age of the child and season of the year, a decision can be made concerning the antibiotic treatment.

Our data did not show a significant difference in clinical characteristics between breast-fed adenovirus-infected and negative infants. However, breastfeeding could be behind the decrease in the severity of adenovirus infection, prevalence of adenovirus and associated otitis media in Jordanian children compared to Western countries. [23-24]

Smoking in households was observed in about 61% of the hospitalized adenovirus-infected and 79% of negative patients (Table 2). Although it is not significantly correlated to adenovirus infection in our study, such high rate of smoking in the household may contribute to some of the clinical symptoms observed in patients at the time of admission including hypoxemia, chest in drawing and signs of respiratory distress. Cigarette smoke is a major risk factor increasing the morbidity and mortality rates of adenovirus infection and activating latent adenoviral infection. [25]

In conclusion, this study has demonstrated the prevalence, seasonality of adenovirus, its associated illnesses, and clinical characteristics. This epidemiological information may help in: (i) predicting the beginning and end of adenovirus epidemics, (ii) considering adenovirus in diagnosis of respiratory illnesses in children between September and December each year, (iii) establishing an effective program for the prevention and control of adenovirus infections, and (iv) providing a basis for avoiding inappropriate antibiotic therapies.

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الانتشار والأعراض السريريه لفيروس الأدينو في أطفال الأردن الذين هم تحت المعالجة

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الملخص

الهدف: يسبب فيروس الأدينو التهاب الجهاز التنفسي عند الرضع والأطفال. ولا تتوافر معلومات في الأردن حول التوزيع الموسمي لانتشار هذا الفيروس والأعراض السريرية المرافقة له. ولهذا أجريت هذه الدراسة على 200 طفل تقل أعمارهم عن سنتين في أثناء إقامتهم في المستشفى للمعالجة.

الطريقه: لقد تم الكشف عن فيروس الأدينو في 200 عينه أنفبلعومية باستخدام تقنية الزراعة الخلوية وتحديد التوزيع الموسمي لانتشار هذا الفيروس وارتباطه بالعوامل الجوية من درجة الحرارة وسقوط الأمطار والرطوبة النسبية والأعراض السريرية.

النتيجة: لقد أثبتت الدراسة أصابة 11,5% من هؤلاء المرضى بفيروس الأدينو، كما أثبتت حدوث الإصابات لمعظم المجموعات العمرية، وكان أعلى حدوث لها في المجموعة العمرية ما بين 7–9 شهور، وكان التعبير الأوضح للإصابة بمرض ذات الرئة والقصبات. لقد شوهدت الحمى (38 مئوياً شرجياً) عند 74% من المرضى المصابين بفيروس الأدينو، في حين لم يكن هنالك فرق بين المرضى المصابين بفيروس الأدينو والمرضى غير المصابين به من حيث نقص أكسجة الدم، تسارع التنفس، السحب الضلعي والخراجز. وقد شوهدت الارتشاحات الخلالية على صورة الصدر الشعاعية على نحوٍ أكبر (أصغر من 0,05) عند المرضى غير المصابين به. ويقع التوزيع الموسمي لانتشار هذا الفيروس في الفترة ما بين فصل الخريف وأول فصل الشتاء. حيث بدأت الإصابة بفيروس الأدينو في أيلول ووصلت إلى قمتها في كانون الأول واختفت في الربيع والصيف. هذا التوزع لم يكن مرتبطاً على نحوٍ ملحوظ بدرجة الحرارة وسقوط الأمطار والرطوبة النسبية.

الخلاصة: إن هذه الدراسة يمكن أن تساعد على أخذ فيروس الأدينو بالاعتبار عند تشخيص الأطفال المصابين بأمراض الجهاز التنفسي في الفترة ما بين فصل الخريف وأول فصل الشتاء من كل عام، كما تساعد على وضع برامج الوقاية والسيطرة على العدوى بهذا الفيروس في الأردن.

الكلمات الدالة: فيروس الأدينو، علم دراسة الأمراض، الأعراض السريرية، الأردن.