



Comparison of clinical characteristics of adenovirus and non-adenovirus pneumonia in children

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Forty-eight cases of adenovirus pneumonia in children were treated in the Department of Pediatrics of Taipei Veterans General Hospital from January 1998 through December 2000. The clinical characteristics of these patients were compared with those of a control group of 70 patients with non-adenovirus pneumonia mostly caused by *Mycoplasma pneumoniae* and other viruses during the same period. No difference was found between the adenovirus and non-adenovirus groups in age, sex, duration of fever, and hospitalization days. Chest retraction and extrapulmonary manifestations were significantly more common in the adenovirus group, especially conjunctivitis, gastroenteritis, lymphadenopathy, bleeding diathesis, and exanthema. C-reactive protein levels were significantly higher in the study group than in the control group. In the adenovirus group, 2 patients died and 5 had permanent lung damage after adenovirus infections. No mortality or long-term sequelae were found in the non-adenovirus group. Adenovirus may cause diseases manifesting predominantly as fever and lower respiratory tract infection that may require hospitalization. Extrapulmonary manifestations were observed in more than half of children with adenovirus infections. Adenoviral pneumonia can be fatal and permanent lung damage may be noted during the follow-up period.

Key words: Adenovirus, extrapulmonary manifestations, pneumonia

Acute respiratory infections caused predominantly by viruses are a leading cause of serious illness and death in children. Adenovirus has been shown to have an important role in the etiology of severe acute respiratory disease, particularly in infants and young children [1]. Adenovirus is responsible for a broad spectrum of diseases in children ranging from mild or even asymptomatic infections to those that are severe and sometimes fatal. The most common manifestations resulting from adenovirus infection involve the respiratory and gastrointestinal tracts, but cardiac, neurological, cutaneous, urinary, and lymphatic manifestations also occur.

Adenovirus infections occur worldwide in the form of epidemic, endemic, or sporadic disease, causing 2% to 7% of respiratory tract infections in children in the first 5 years of life [2]. Most of the infections caused by these viruses are mild upper respiratory illnesses, but the lower respiratory tract may also be involved. Adenoviruses are responsible for 5% to 11% of viral pneumonia and bronchiolitis in infants and children [3-6]. The attack rate is higher in the very young and those

with environmental risk factors, such as daycare attendance, overcrowded living conditions, and poor socioeconomic status. Host factors such as malnutrition, anatomic anomalies, metabolic or genetic disease, chronic heart or lung disease, and immunologic deficiencies contribute to the severity of adenovirus disease [7].

The severe lower respiratory tract infections caused by adenovirus are often accompanied by extrapulmonary manifestations, including encephal meningitis, myocarditis, renal involvement, hepatomegaly, hemorrhagic tendency, peripheral edema, gastroenteritis, and exanthema [8-11].

This study describes the clinical and roentgenographic characteristics of pneumonia caused by adenovirus in 48 patients. Findings in these patients were compared with those of a group of children hospitalized for pneumonia of other origins during the corresponding period of time.

Materials and Methods

During the period from January 1998 through December 2000, children with pneumonia admitted to the Department of Pediatrics of Taipei Veterans General Hospital who had adenovirus isolates and a rise in the titer of complement fixation antibody to adenovirus of 4 fold or more were included in this retrospective study.

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The diagnosis of pneumonia was based on the simultaneous finding of (1) fever ($\geq 38^{\circ}\text{C}$) and/or respiratory symptoms and (2) infiltrate on chest radiography. The characteristics of these patients were compared with 40 boys and 30 girls admitted to the Department during this same period for pneumonia, but for whom adenovirus infection was ruled out by virologic and serologic tests.

Demographic data and clinical manifestations of the patients in the 2 groups were compared. These data include age, sex, symptoms and signs, duration of fever, duration of hospitalization, laboratory findings, concomitant extrapulmonary manifestations, the outcome, and the sequelae.

Virus isolation

Throat swab specimens were collected on admission and processed for viral isolation. The specimens were inoculated into human esophageal type 2 (HEP-2) cell culture. These cell cultures were maintained in Eagle's minimum essential medium with 2.5% inactivated calf serum. The cell cultures were maintained at 37°C for 14 days. The inoculated cultures were examined 2 to 3 times a week, and the media were changed every 7 days. The diagnosis of adenovirus infection by characteristic cytopathic effect was confirmed by indirect immunofluorescent antibody assays (DAKO, Cams, UK).

Serologic tests

Antibody determinations of paired serum specimens were carried out by complement fixation. A 4-fold or greater rise in titer over a 2- to 3-week period was considered diagnostic of a recent adenoviral infection. In many cases serum specimens were also tested with antigens of influenza virus types A and B, parainfluenza virus types 1 to 3, respiratory syncytial virus, Coxsackie virus B types 1 to 5, and *Mycoplasma pneumoniae*.

Statistical analysis

Results are presented as mean \pm standard deviation. The differences between the adenovirus and non-adenovirus group were analyzed using independent-samples *t* test and chi-square analysis. A *p* value of less than 0.05 was considered statistically significant.

Results

Study populations

A total of 48 children, 25 boys and 23 girls, had a diagnosis of adenovirus pneumonia, isolation of adenovirus, and a rise in the titer of complement fixation

antibody to adenovirus of 4-fold or more during the study period. No significant elevation in other virus antibody titers was found in these patients. The mean age of the adenovirus group was 4.1 ± 2.31 years (range, 4-139 months). A total of 70 children, 40 boys and 30 girls, had a diagnosis of non-adenovirus pneumonia confirmed by virologic and serologic tests during the study period. In the non-adenovirus group, *M. pneumoniae*, respiratory syncytial virus, rhinovirus, and parainfluenza virus were found in 40, 10, 3, and 2 cases, respectively. The mean age of the non-adenovirus group was 4.01 ± 2.39 years (range, 7-144 months). No significant difference was found in the mean age at onset of pneumonia and the sex ratio between these 2 groups.

Clinical manifestations

All of the patients in the 2 groups had symptoms of fever and cough. There was no significant difference in the mean duration of fever between the 2 groups— 6.85 ± 2.26 days (range, 3-12 days) in the adenovirus group and 6.19 ± 4.23 days (range, 2-12 days) in the non-adenovirus group. Two patients in the adenovirus group had a biphasic fever pattern, which was not found in the non-adenovirus group.

Patients of the adenovirus group presented subcostal, intercostal, or suprasternal retractions more frequently than patients in the non-adenovirus group ($p < 0.01$). No significant difference was found in the respiratory rate between these 2 groups. Auscultations of patients in the 2 groups all showed coarse breathing sounds with rales. Furthermore, 10 patients in the non-adenovirus group had wheezing compared with only one patient in the adenovirus group ($p = 0.03$). No significant difference was found in the frequency of respiratory stridor. The mean level of C-reactive protein (CRP) in the adenovirus group (6.71 ± 4.99 mg/dL) was significantly higher than that of the non-adenovirus group (2.78 ± 3.59 mg/dL) ($p < 0.001$).

There was no significant difference in the mean duration of hospitalization between the adenovirus group (mean, 5.69 ± 4.10 days; range, 3-26 days) and the non-adenovirus group (mean, 4.73 ± 2.01 days; range, 3-12 days). The demographic data, presenting symptoms and signs, duration of hospitalization, and CRP levels of the 2 groups are shown in Table 1.

The roentgenologic pulmonary changes in the adenovirus group included pneumonic infiltrations (48/48), pneumothorax (2/48), and pleural effusion (1/48).

Extrapulmonary manifestations

Extrapulmonary manifestations in both groups included conjunctivitis, otitis media, gastroenteritis,

Table 1. Demographic data, presenting symptoms and signs, duration of hospitalization, and C-reactive protein level of adenovirus and non-adenovirus pneumonia in children

Characteristic	Adenovirus group n = 48 (%)	Non-adenovirus group n = 70 (%)	<i>p</i>
Male/female	25/23	40/30	0.59
Mean age, year	4.10 ± 2.31	4.01 ± 2.39	0.84
Duration of fever, days	6.85 ± 2.26	6.19 ± 4.23	0.32
Duration of hospitalization, days	5.69 ± 4.10	4.73 ± 2.01	0.09
Presenting symptom/sign			
Cough	48 (100)	70 (100)	
Tachypnea	5 (10.4)	2 (2.9)	0.09
Retraction	5 (10.4)	0	0.006
Rales	48 (100)	70 (100)	
Wheezing	1 (2.1)	10 (14.3)	0.03
Stridor	2 (4.2)	0	0.09
CRP levels, mg/dL	6.71 ± 4.99	2.78 ± 3.59	<0.001

Abbreviation: CRP = C-reactive protein

lymphadenopathy, bleeding diathesis (melena, hematemesis, bloody tracheal secretions, or hemorrhage in puncture sites), anemia (hemoglobin <10 mg/dL), hepatomegaly, splenomegaly, exanthema, neurologic signs (lethargy to coma, localized to generalized tonic-clonic seizures, uncoordinated movements of the extremities), and renal signs (granular casts, red and white blood cells and increased protein loss in urine). Extrapulmonary manifestations were present in 30 patients in the adenovirus group, but in only 19 patients of the non-adenovirus group ($p < 0.001$). Significantly higher frequencies of conjunctivitis; gastroenteritis, lymphadenopathy, bleeding diathesis, and exanthema were found in the adenovirus group. No significant difference in other extrapulmonary manifestations was found between the 2 groups. The extrapulmonary manifestations of the patients are shown in Table 2.

Complications, outcome, and sequelae

Four patients in the adenovirus group were transferred to the intensive care unit because of severe pulmonary infections and extrapulmonary manifestations. Two of them were intubated and developed pneumothorax during the hospitalization course. However, none of the patients in the non-adenovirus group required intensive care. In the adenovirus group, 2 cases were fatal, 41 recovered without any serious complications, and permanent sequelae of bronchiolitis obliterans was noted in 5 patients after recovery. In the non-adenovirus group, all 70 patients recovered smoothly after treatment without any permanent complication, and no fatal cases were found. Patients with adenovirus infections had a significantly more serious sequelae than patients in the non-adenovirus group ($p < 0.01$). The complications, outcome, and sequelae of these 2 groups are shown in Table 3.

Table 2. Extrapulmonary manifestations of adenovirus and non-adenovirus pneumonia in children

Extrapulmonary manifestation	Adenovirus group n = 48 (%)	Non-adenovirus group n = 70 (%)	<i>p</i>
Conjunctivitis	10 (20.8)	3 (4.3)	0.005
Otitis	8 (16.7)	10 (14.3)	0.72
Gastroenteritis	12 (25.0)	5 (7.1)	0.007
Lymphadenopathy	5 (10.4)	0	0.006
Bleeding diathesis	4 (8.3)	0	0.01
Anemia	2 (4.2)	2 (2.9)	0.70
Hepatomegaly	2 (4.2)	0	0.09
Splenomegaly	2 (4.2)	0	0.09
Neurological sign	2 (4.2)	1 (1.4)	0.35
Renal sign	1 (2.1)	0	0.23
Exanthema	15 (31.3)	6 (8.6)	0.002
Total	30 (62.5)	19 (27.1)	<0.001

Table 3. Complications, outcome, and sequelae of adenovirus and non-adenovirus pneumonia in children

	Adenovirus group n = 48 (%)	Non-adenovirus group n = 70 (%)
Complication		
Pneumothorax	2 (4.2)	0
Outcome		
Survival	46 (95.8)	70 (100)
Death	2 (4.2)	0
Sequelae		
Bronchiolitis obliterans	5 (10.4) ^a	0

^a $p < 0.01$.

Discussion

Since initially described in the 1950s, adenovirus has been known as a common cause of childhood respiratory illness [1]. The onset of illness is usually acute, characterized by fever, coryza, and severe pneumonia. In this study, virologic examinations indicated that all of the 48 patients in the adenovirus group had an adenovirus infection during the observation period. The pneumonic infections associated with adenovirus infection were much more severe than those in the non-adenovirus pneumonia group. High fever persisted in many of the severe cases for 10 days or longer and did not respond to antibiotic treatment.

In this study, chest retractions were more prominent in the adenovirus group than in the non-adenovirus group, suggesting that adenovirus infection can cause much more severe lung function impairment than non-adenovirus infection. Further, non-adenovirus group patients presented with wheezing more frequently than adenovirus group patients, suggesting that a child with pneumonia who has wheezing on auscultation is less likely to have adenovirus infection. It is interesting that the values of CRP were significantly higher in the adenovirus group than in the non-adenovirus group, although the reason for this finding remains unclear.

Extrapulmonary manifestations were more frequent in children with adenovirus infection than in those with non-adenovirus infection group, an observation that has also been made by previous studies [8-11]. Conjunctivitis, gastroenteritis, lymphadenopathy, bleeding diathesis, and exanthema were frequent findings in patients with adenovirus infections in this study. This finding suggested that as the number of extrapulmonary manifestations increases, the possibility of adenovirus infection may also increase. Bleeding tendency and anemia may be a sign of intravascular coagulation, which has been reported to occur in several viral diseases [12].

Two patients with adenovirus infection in this series had neurological manifestations, including

meningismus and meningoencephalitis. Despite vigorous treatment, these patients developed pneumothorax, became ventilator dependent, and died from acute respiratory distress syndrome after prolonged ventilator support (case fatality rate, 4.2%). One of these 2 patients had cerebral palsy and had been bed-ridden with malnutrition for 4 years, and the other one had chronic hepatitis. The reason for the increased severity in some adenovirus infections is not clear. Certain host risk factors have been suggested to have an important role in the development of severe or fatal infections. Children with immunodeficiency states, malnutrition, or a preceding viral illness have been considered to be more susceptible to the development of a severe disease [13-16]. Although none of the children in this study was considered immuno-compromised, the possible existence of a basic immunologic defect in some patients cannot be ruled out because no immunologic studies were performed. Malnutrition was present in one of the 2 children who died and this might have been an important factor in the development of his fatal infection.

Five patients with adenovirus infections progressed to bronchiolitis obliterans during the follow-up period. None of these patients had respiratory or other illnesses before developing pneumonia associated with adenovirus infection. This finding suggested that adenovirus infections may damage the bronchial epithelium, directly or indirectly, and thereby initiate a series of events leading to the development of bronchiolitis obliterans and impaired lung function.

In conclusion, adenovirus may cause disease manifesting predominantly as fever and lower respiratory tract infection, which may require hospitalization in severe cases. Extrapulmonary manifestations are observed in more than half of the children with adenovirus infections. Although most patients with adenoviral pneumonia recover after appropriate supportive treatment, fatal cases and permanent lung damage may occur.

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