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Original Article

A cluster of adenovirus serotype 3 infections in children in northern Taiwan: clinical features and laboratory findings

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Background and Purpose: To define clinical manifestations and laboratory findings of adenovirus serotype 3 infections in children.

Methods: A total of 499 children diagnosed with adenovirus infections based on throat virus cultures were treated in Chang Gung Children's Hospital from January 2004 to May 2005. Serotypes were determined in 197 strains, of which majority were serotype 3 (n = 147; 107 inpatients and 40 outpatients). Demographics, clinical presentations, and laboratory findings of the inpatients and demographics only of the outpatients were evaluated.

Results: The mean age was 4 years and 7 months (range, 5 months to 12 years). Adenovirus serotype 3 infections were identified in 74.6% of the 197 children examined between January 2004 and May 2005. The mean time lag between specimen collection and a positive culture result was 8.3 days. The 3 most common symptoms were fever (100.0%), cough (87.9%), and rhinorrhea (73.8%). The mean duration of fever was 6 days, and the mean duration before admission was 4 days. The mean length of hospital stay was 5.4 days. The 3 most common diagnoses were tonsillitis/pharyngitis (43.0%), pneumonia/bronchopneumonia (32.7%), and acute otitis media (6.5%). Fifteen children had documented bacterial coinfection. Leukopenia (white blood cell [WBC] <5000/mm^3) was noted in 2 patients (2.1%) and leukocytosis (WBC ≥15,000/mm^3) in 28 patients (30.4%). Of the 92 children with serum C-reactive protein level measurements, 74 children (80.4%) had a serum C-reactive protein level >40 mg/L. Although 69 (64.0%) of the 107 hospitalized children never received antibiotic therapy, the outcomes were excellent.

Conclusion: By recognizing that children with adenoviral infections may present with prolonged high fever, leuokocytosis, and elevated C-reactive protein levels, mimicking symptoms of bacterial infections, clinicians will be able to avoid the unnecessary prescription of antibiotics to these patients.

Key words: Adenoviridae; Bacterial infections; Child

Introduction

Adenovirus is an important cause of acute respiratory illness in children, and is implicated in 4-10% of pneumonia, 2-10% of bronchiolitis, and 3-9% of croup [1]. There are also other manifestations, such as conjunctivitis, gastroenteritis, hematuria, neurological symptoms, and disseminated diseases [1-6].

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There are at least 49 recognized serotypes; some serotypes are more pathogenic than others. Severe diseases have been noted in association with adenovirus types 1-7, 7a, 8, 19, 21, 35, etc. [1,6]. Most laboratories do not serotype adenovirus isolates, which makes it more difficult to identify outbreaks of infection caused by a specific type of adenovirus occurring in the community [7] or hospital [8,9]. Lower respiratory tract infections caused by adenoviruses can occur endemically or in epidemics. In most studies, adenoviruses are isolated endemically throughout the year [10,11].

Host factors, such as malnutrition, anatomic abnormalities, metabolic or genetic diseases, chronic heart or lung disease, and immunological deficiencies contribute to the severity of adenovirus disease [12,13]. Infections commonly occur in children, and acute infection may lead to long-term respiratory sequelae, including bronchiectasis and hyperlucent lung or McLeod syndrome [14]. Adenovirus is reported to be the primary viral agent that leads to death in children [15].

Surveillance data showed an increase in the number of adenoviral isolates in our virology laboratory during the winter of 2004 and most isolates revealed serotype 3 on subsequent serotyping. These findings prompted us to review the clinical features of children with adenovirus serotype 3 infections, who were treated at the Chang Gung Children's Hospital, by comparing these with non-serotype 3 infections.

Methods

Case enrollment

From January 2004 to May 2005, a total of 499 children with adenovirus infections, based on throat virus culture, were treated in Chang Gung Children's Hospital. Serotypes were determined in 197 children and were included in this study. Of the 197 patients, 143 were inpatients and 54 outpatients. Serotype 3 was identified in 147 children, of whom 107 were hospitalized.

Medical records of these patients were reviewed retrospectively. Only demographics were collected and analyzed from outpatients. On the other hand, data collected from inpatients included demographics, underlying disease, adenovirus serotype, clinical diagnosis, clinical manifestations, laboratory findings, and results of radiological examinations. All data were expressed as mean ± standard deviation.

Definition

Acute otitis media was defined by the presence of fluid in the middle ear, accompanied by acute signs of illness. The definition of bronchiolitis was wheezing and crackles audible in both the lungs of a child less than 2 years of age, with respiratory illness and a compatible chest X-ray finding. Fever of unknown origin was defined as a child with fever of at least 7 days' duration, in whom no diagnosis was apparent after initial work-up either in the hospital or a clinic. Pharyngitis could feature concurrent conjunctivitis and fever, and was defined as pharyngoconjunctival fever. Pneumonia was defined by its clinical manifestations (fever, cough, tachypnea, and chest pain) and a compatible chest radiological finding (interstitial infiltration, peribronchial cuffing, or lobar consolidation). A simple febrile seizure was fever (body temperature >38°C) associated with a seizure that was generalized, tonic-clonic, and lasted from a few seconds to 10 min. The diagnosis of encephalitis was based on altered consciousness or seizure associated with fever. The diagnosis was supported by electroencephalogram (EEG).

Virological studies

In our virology laboratory, virus isolation was carried out by tissue culture [16] and each respiratory specimen was inoculated into 4 cell lines, including the human epidermoid carcinoma cells, canine kidney cells, human embryonic lung fibroblasts, and rhesus monkey kidney cells. Cultures were maintained in minimal essential media containing antibiotics and incubated at 33°C, rotated at 12 revolutions per h. All cultures were observed daily for cytopathic effects. Rhesus monkey kidney cell cultures were tested for hemadsorption with 0.5% guinea pig erythrocytes at 4°C at 3-day intervals.

Serotyping

After recovery of a clinical isolate on tissue culture, further serotype analyses by polymerase chain reaction (PCR) and restriction fragment length polymorphism were performed in a reference virology laboratory at the Center for Disease Control, Taiwan. Briefly, the primer pair, AdnU-S (5'-TTCCCCATGGCNCACA ACAC-3') and AdnU-A (5'-GCCTCGATGACGCCG CGGTG-3'), was used to amplify a 956-bp sequence in the hexon region. PCR was carried out in a final volume of 50 μL containing 10 mM Tris-hydrogen chloride, 50 mM potassium chloride, 1.5 mM magnesium chloride, 0.2 mM of deoxynucleoside triphosphate mix, 0.5 μM of each primer, 1 U of Taq DNA polymerase, and 5 μL of extracted DNA.

For the analysis of representative strains of each genome type, PCR products were subjected to digestion with 12 restriction enzymes — BamHI, Bcl I, Bgl I, Bgl II, Bst EII, Eco RI, Hind III, Hpa I, Sal I, Sma I, Xba I, and Xho I — purchased from Boehringer Mannheim GmbH, Mannheim, Germany, and New England Biolabs, Beverly, MA, USA. The restriction fragment length polymorphism patterns were identified according to the patterns of genotypes previously reported [17].

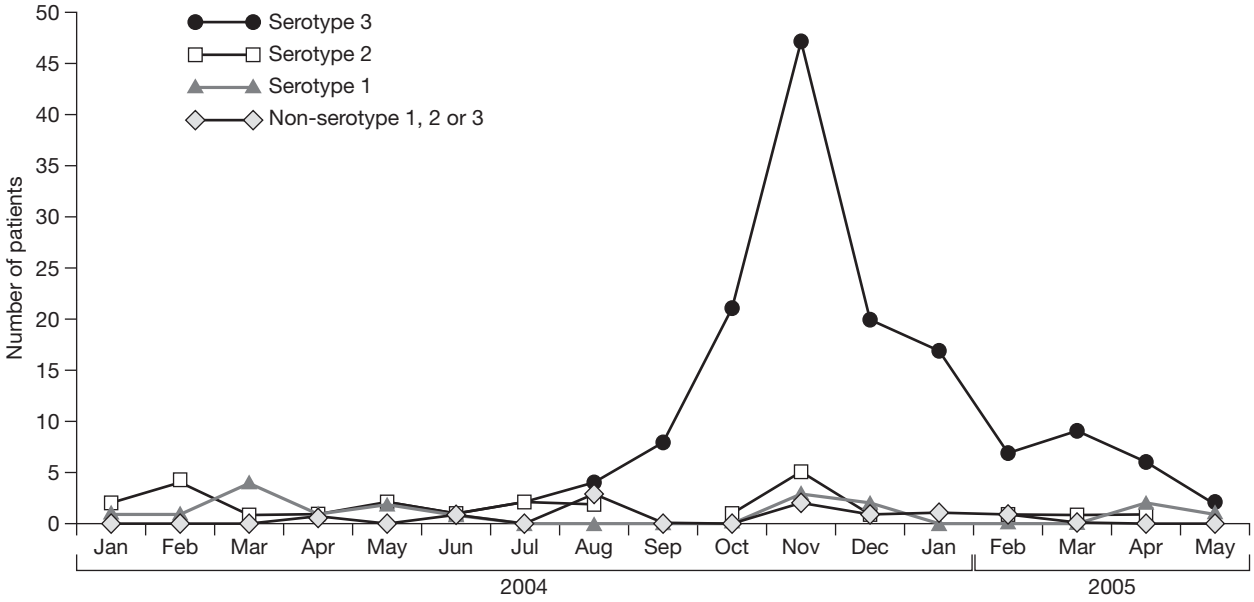

Fig. 1. Serotypical presentation of the monthly incidence of adenovirus infections in children treated at the Chang Gung Children's Hospital from January 2004 to May 2005.

Statistical analysis

Analysis of variance were used to analyze the differences between patients with adenovirus serotype 3 and non-serotype 3 infections. Categorical data was analyzed by Pearson's chi-squared test. The continuous variable was analyzed by Student's *t* test. A p value <0.05 was considered statistically significant. Analyses were done with the Statistical Package for the Social Sciences (SPSS) for Windows (Version 10.1; SPSS, Chicago, IL, USA) and SAS (Version 8.0; SAS Institute Inc., Cary, NC, USA).

Results

Epidemiology

Of the 197 children in whom serotyping was carried out, adenovirus infections were identified in 121 (60%) during the winter of 2004 (from October 2004 to January 2005) and adenovirus activity was seen to peak in November 2004 (29%) during the study period (Fig. 1). The mean age of inpatients and outpatients was 4 years and 2 months, and 4 years and 3 months, respectively. Three children (1.5%) were <6 months of age, 24 (12.2%) were between 6-23 months of age, and 136 (69.0%) were <60 months of age. The proportion of children younger than 5 years old was higher in inpatients than in outpatients, but did not reach any significant difference (72.2% vs 60.4%, p=0.068). Demographic data are shown in Table 1.

Of the 197 isolates, type 3 was the most common serotype found and accounted for 147 isolates (74.6%). Other serotypes identified included type 1 in 16 children, type 2 in 24 children, type 5 in 2 children, type 7 in 3 children, and type 6, 8, and 35, in 1 child each. Two children had 2 serotypes identified. One child had both adenovirus serotypes 1 and 3 isolated from the throat swab; the other showed adenovirus serotype 3 in the throat virus culture and serotype 7 in the rectal virus culture. These 2 cases were excluded when comparing the association between serotypes and clinical presentations.

Twenty six hospitalized children (18.2%) had underlying conditions, including asthma and/or allergic rhinitis in 9 children, microcytic anemia in 4 children (alpha-thalassemia in 1), premature birth in 2 children (at the age of 2 years and 2 months, and 1 year, respectively), developmental delay in 2 children, and 1 child each showing arrhythmia, congenital tracheal stenosis, atrial septal defect, chronic sinusitis, small size for gestational age (at the age of 5 years), glucose-6-phosphate dehydrogenase deficiency, carotid hemangioma, seizure disorder, and tic disorder.

Children with adenovirus serotype 3 infections were significantly younger than children with adenovirus non-serotype 3 infections (mean age, 4 years and 7 months vs 3 years, p<0.001; aged less than 5 years old: 59.2% vs 87.5%, p=0.003). No significant difference was noted in terms of patients with underlying diseases (15.9% vs

Table 1. Demographic data of hospitalized children with adenovirus infections stratified by serotype

Characteristic	Adenovirus serotypes				
	Type 1	Type 2	Type 3	Other types	Total
No. of children	16	24	147	10	197
No. of children hospitalized	13	17	107	6	143
Children with underlying disease (no. [%])	2 (15.4)	5 (29.4)	17 (15.9)	2 (33.3)	26 (18.2)
Hospital stay (days)[a]	5.1 ± 2.1	5.2 ± 2.8	5.4 ± 2.0	5.3 ± 1.2	5.3 ± 2.1
Age					
Range (months)	7-83	6-83	5-146	18-76	5-146
Mean (months)[a,b]	37.3 ± 21.9	31.2 ± 14.2	54.8 ± 23.4	61.0 ± 34.6	50.3 ± 24.2
<2 years (no. [%])	3 (18.8)	9 (37.5)	10 (6.8)	1 (10.0)	23 (11.7)
<5 years (no. [%])	13 (100.0)	23 (95.8)	87 (59.2)	8 (80.0)	131 (66.5)
Male:female ratio	1.7:1.0	1.4:1.0	1.3:1.0	2.3:1.0	1.3:1.0

[a]Mean ± standard deviation.

[b]Patients with serotype 3 infections were significantly younger than those with non-serotype 3 infections (p<0.001).

23.5%, p=0.309) and hospitalization rate (72.8% vs 70.8%, p=0.793) between the 2 groups.

Clinical presentations

The most common symptoms in the 107 hospitalized children with adenovirus serotype 3 infections were fever (100.0%), cough (87.9%), and rhinorrhea (73.8%) [Table 2]. The average peak body temperature was 39.3°C. High fever (>39°C) was noted in 81 inpatients (75.7%). The mean duration of fever was 6.1 ± 2.2 days (range, 1-13 days), with 4.1 ± 1.8 days before admission and 2.0 ± 1.6 days after admission. The mean duration of hospitalization was 5.4 ± 2.0 days (range, 2-16 days). Gastrointestinal symptoms were noted in 55 inpatients (51.4%), including diarrhea in 26 patients, vomiting in 24, and abdominal pain in 20. Eleven patients (10.3%) complained of myalgia. Sixteen patients (15.0%) had cervical lymphadenopathy, multiple and bilateral in most cases. Macular/maculopapular rashes were observed in 9 patients (8.4%). There was no significant difference

Table 2. Clinical characteristics of hospitalized children with adenovirus infections

Characteristic	Adenovirus serotypes			p
	Type 3 (n = 107) No. (%)	Other types (n = 34) No. (%)	Total[a] (n = 141) No. (%)	
Respiratory symptoms				
Cough	94 (87.9)	32 (94.1)	126 (89.4)	0.52
Rhinorrhea	79 (73.8)	26 (76.5)	105 (74.5)	0.76
Sore throat	40 (37.4)	7 (20.6)	47 (33.3)	0.07
Dyspnea/tachypnea	7 (6.5)	2 (5.9)	9 (6.4)	1.00
Constitutional symptoms				
Chills	14 (13.1)	5(14.7)	19 (13.5)	0.81
Headache	9 (8.4)	1 (2.9)	10 (7.1)	0.45
Peak body temperature (°C)	39.3	39.2	39.3	-
High fever >39°C	81 (75.7)	22 (64.7)	103 (73.0)	0.21
Duration of fever (days)[b]	6.1 ± 2.2	5.9 ± 3.0	6.0 ± 2.4	0.81
Extrapulmonary symptoms				
Diarrhea	26 (24.3)	9 (26.5)	35 (24.8)	0.80
Vomiting/nausea	24 (22.4)	5 (14.7)	29 (20.6)	0.33
Abdominal pain	20 (18.7)	5 (14.7)	25 (17.7)	0.60
Skin rash	9 (8.4)	1 (2.9)	10 (7.1)	0.45
Lymphadenopathy	16 (15.0)	7 (20.6)	23 (16.3)	0.44
Myalgia	11 (10.3)	1 (2.9)	12 (8.5)	0.29

[a]Two children had 2 serotypes identified and were excluded from the comparison.

[b]Mean ± standard deviation.

in clinical symptoms and signs between children with serotype 3 and non-serotype 3 infections.

Neurological manifestations were noted in 2 patients with adenovirus serotype 3 infections. One child had febrile seizure. The other was admitted under the impression of pneumonia. He became drowsy 4 days after admission and an EEG examination disclosed diffused cortical dysfunction with a focal epileptiform discharge over the right parietal area. His consciousness became normal 2 days later. Neurological manifestations were also noted in 2 patients with adenovirus non-serotype 3 infections. One child had febrile seizure. The other presented with visual hallucination and fever, and EEG examination indicated diffused cortical dysfunction; two different serotypes of adenovirus were identified from different sites (throat, serotype 3; rectum, serotype 7) in this case.

The most common initial diagnosis of hospitalized children due to serotype 3 infection was tonsillitis (38.3%), followed by pneumonia (31.8%) and acute otitis media (5.6%), while the most common final diagnoses of hospitalized children were tonsillitis/pharyngitis (43.0%), pneumonia/bronchopneumonia (32.7%), and acute otitis media (6.5%). The final diagnoses of inpatients due to serotype 3 and non-serotype 3 infections are shown in Table 3. No significant difference was noted between the 2 groups.

Concomitant viral infection was noted in 3 hospitalized children with serotype 3 infections. One child had fever, respiratory symptoms and diarrhea, and also had a positive rotavirus antigen test. The second child had both herpes simplex virus and adenovirus isolated from throat virus culture, with a final diagnosis of tonsillitis and acute otitis media. The remaining one with a diagnosis of hand, foot, and mouth disease had both enterovirus and adenovirus isolated from throat virus culture.

Concomitant or secondary bacterial infections/colonization were identified in 15 patients with serotype 3 infections, including *Mycoplasma pneumoniae* infection (by positive *M. pneumoniae* immunoglobulin M) in 8, group A *Streptococcus* pharyngitis by a positive rapid antigen test (QuickVue+ Strep A; Quidel, San Diego, CA, USA) in 4 patients, pneumonia probably caused by *Streptococcus pneumoniae* (1 by a positive Binax NOW test [Binax, Portland, ME, USA] and 1 by a sputum culture that yielded both *S. pneumoniae* and *Haemophilus influenzae*) in 2, and pneumonia probably caused by *H. influenzae* (by sputum culture) in 1.

Laboratory findings

Excluding the 15 patients with concomitant or secondary bacterial infections, the mean value of white blood cell (WBC) count on admission was 12,602 ± 4977/mm^3 (Table 4). Two cases of the 92 (2.2%) had a leukocyte count of <5000/mm^3. Leukocytosis (WBC >15,000/mm^3) was noted in 28 patients (30.4%). One inpatient had thrombocytopenia (platelet count <10^5/mm^3) and 6 patients had thrombocytosis (platelet count >40 × 10^5/mm^3). Serum alanine aminotransferase and aspartate aminotransferase levels were obtained in 14 and 23 patients, respectively, and were normal.

Serum C-reactive protein (CRP) concentration was measured in 107 patients. Excluding the patients with concomitant or secondary bacterial infections, 74 (80.4%) of 92 cases had a serum CRP level greater than 40 mg/L, mimicking bacterial infections. Thirty four of 92 cases (37.0%) had a serum CRP level greater than 100 mg/L. Only 5 (5.4%) of 92 children had a normal CRP concentration (<10 mg/L). Compared to

Table 3. Final diagnoses of hospitalized children with adenovirus infections

Diagnosis	Adenovirus serotypes			*p*
	Type 3 (n = 107) No. (%)	Other types (n = 34) No. (%)	Total[a] (n = 141) No. (%)	
Pharyngoconjuctival fever	6 (5.6)	3 (8.8)	9 (6.4)	0.45
Tonsillitis/pharyngitis	46 (43.0)	18 (52.9)	64 (45.4)	0.31
Acute otitis media	7 (6.5)	1 (2.9)	8 (5.7)	0.68
Bronchiolitis/bronchitis	3 (2.8)	3 (8.8)	6 (4.3)	0.15
Pneumonia	35 (32.7)	6 (17.6)	41 (29.1)	0.09
Fever of unknown origin	0 (0.0)	2 (5.9)	2 (1.4)	0.06
Febrile seizure	1 (0.9)	1 (2.9)	2 (1.4)	0.43
Encephalitis	1 (0.9)	0 (0.0)	1 (0.7)	1.00
Herpangina/hand, foot, and mouth disease	3 (2.8)	1 (2.9)	4 (2.8)	1.00
Mixed infections	18 (16.8)	5 (14.7)	23 (16.3)	0.25

[a]Two children had 2 serotypes identified and were excluded from the comparison.

Table 4. Laboratory findings of patients with adenovirus infections

Characteristic	Adenovirus serotypes			*p*
	Type 3 (n = 92)	Other types (n = 30)	Total[a] (n = 122)	
WBC count (/mm^3)[b]	12,602 ± 4977	14,093 ± 4253	12,968 ± 4835	0.143
Leukocytosis >15,000/mm^3 (no. [%])	28 (30.4)	13 (43.3)	41 (33.6)	0.194
Leukopenia <5000/mm^3 (no. [%])	2 (2.2)	0 (0)	2 (1.6)	1.000
CRP (mg/L)[b]	89 ± 57	60 ± 45	82 ± 55	0.012
CRP >40 mg/L (no. [%])	74 (80.4)	18 (60.0)	92 (75.4)	0.024
Platelet (× 10^3/mm^3)[b]	257.0 ± 76.9	283.2 ± 120.4	263.4 ± 89.8	0.167

Abbreviations: WBC = white blood cell; CRP = C-reactive protein

[a]Two children with 2 serotypes identified and 19 patients with documented concomitant or secondary bacterial infections were excluded.

[b]Mean ± standard deviation.

the children hospitalized with non-serotype 3 infections, children with serotype 3 infections were significantly more likely to have a serum CRP values >40 mg/L (80.4 % vs 60.0%, $p<0.024$).

Chest radiographs of 75 patients were available for review. Bilateral peribronchial infiltration and perihilar infiltration were observed in 37 children (49.3%). Consolidation that mimicked bacterial pneumonia was identified in 11 children (14.7%). None had pleural effusions or complicated pneumonia.

Treatment and outcome

Among the 107 hospitalized children with serotype 3 infections, 69 patients (64.5%) received antibiotic therapy, including a penicillin, aminoglycoside, cephalosporin, or macrolide. Sixteen of these 107 children received only empiric antibiotics (the duration was no more than 3 days). None had received an antiviral agent or intravenous immunoglobulin. The recovery of all hospitalized children was uneventful.

Discussion

Two previous studies regarding adenoviral epidemiology in southern Taiwan showed that adenovirus types 3 and 7 were the 2 major serotypes identified between 1999 and 2000 [17]. Later, adenovirus serotype 4 (57%) was found to dominate in 2001, while serotype 3 became dominant (46%) again in 2002 [18]. The current study indicated that adenovirus serotype 3 prevailed in northern Taiwan between 2004 and 2005, and clustered in the winter of 2004. The current study also showed that two-thirds of the patients with adenoviral infections were less than 5 years of age, particularly those with non-serotype 3 infections, which was similar to previous reports [6,19,20].

Certain serotypes of adenovirus, including serotype 3, are reported to be associated with severe diseases in children, but the reasons behind this are not clear yet. Children with immunodeficiency, malnutrition, or a preceding viral illness are considered more susceptible to the development of a severe disease [1]. In this study, 18.2% patients had underlying diseases, but none of these patients were regarded as immunocompromised and none developed severe disease subsequently. The incidence of severe or disseminated diseases in immunocompetent children was shown to be around 1.1-1.5% in previous studies [5,21], so the most probable reason for the contrary findings of this study could be the case number of the current study being too small to reveal a severe case. However, a previous report from the same institute indicated that from July 1999 to September 2000, 9 children with severe adenovirus infection were identified. Seven of these were caused by adenovirus serotype 3 [21]. The mean age was 22 months (range, 5-50 months), which was significantly younger than that of patients in the current study (50.7 ± 24.5 months in hospitalized children; range, 5-146 months). This may partly explain the different outcomes. A retrospective review by Munoz et al [5] also revealed that immunocompetent children with disseminated adenovirus disease were significantly younger, all <3 years of age.

Compared with those with adenovirus non-serotype 3 infections, patients with adenovirus serotype 3 infections had a significantly higher serum CRP level, suggesting more severe inflammation; the latter were also relatively older. However, no other significant differences were noted between the 2 groups in terms of demographics, clinical presentations, laboratory findings, and clinical diagnoses.

In the current study, leukocytosis (WBC >15,000/mm^3) was noted in 33.1% of patients with adenoviral infections

without any detectable bacterial infections, which is infrequently seen in other viral infections and seems to be specific to adenoviral infections. The majority of children with respiratory syncytial virus, parainfluenza, or influenza infections usually have a leukocyte count $<1.5 \times 10^4/mm^3$, while about 25-50% of children with adenoviral infections have leukocyte counts $>1.5 \times 10^4/mm^3$ [3]. Likewise, highly elevated serum CRP levels were noted in patients with adenoviral infections, which is not frequently seen in other viral infections. Appenzeller et al [22] reported that patients with adenoviral infections had higher CRP levels (49 mg/L), in comparison with those suffering from other respiratory viral infections (respiratory syncytial virus, 17 mg/L; parainfluenza virus, 10 mg/L; influenza virus, 23 mg/L). In the current study, 53.6% of patients with adenoviral infections had serum CRP concentrations of >70 mg/L, a value that was previously used as the cut-off point for the identification of clinically undetectable, serious bacterial infections [23]. This might be related to the high interleukin-6 values found in patients with adenoviral respiratory infections [24].

As the clinical features of adenovirus infections are similar to those of bacterial infections, it is not surprising that nearly two-thirds of the patients in this study were treated with antibiotics initially. Tissue culture for viral isolation is not only a slow procedure but also restricted to a few specialized laboratories. Thus, the prescription of unnecessary antibiotics to these patients can only be avoided if clinicians recognize the clinical features and course of the disease early, and at the same time have timely local epidemiologic information about adenoviral infections. A rapid diagnostic tool that can support clinical practice by providing a quick and reliable confirmation of infection is also mandatory.

In conclusion, recognizing that children with adenoviral infections may present with prolonged high fever, leuokocytosis, and elevated CRP levels, similar to bacterial infections, could help clinicians to avoid the unnecessary prescription of antibiotics. Development of a rapid and accurate diagnostic tool for adenovirus detection would also be invaluable.

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