

:

*.

*

= Abstract =

Adenoviral Lower Respiratory Tract Infections in Children; Serotypes and Clinical Characteristics

Seon Hee Shin, M.D., Hoan Jong Lee, M.D.* and Hae Sun Yoon, M.D.

*Department of Pediatrics, College of Medicine, Hallym University,
Department of Pediatrics*, Seoul National University College of Medicine, Seoul, Korea*

Purpose : This study was performed to characterize the epidemiologic and clinical features of acute adenoviral lower respiratory tract infections(LRTIs).

Methods : Virological analysis was done from respiratory specimens obtained from patients with LRTIs hospitalized to other hospitals and referred to the Department of Pediatrics, Seoul National University Children's Hospital(SNUCH) from June 1998 to July 2000. Viral diagnosis was made by isolation of viruses employing HEp-2 cell culture and indirect immunofluorescent staining with monoclonal antibodies. Serotypes of adenoviruses were determined by neutralization test using antiserum for types 1, 2, 3, 4, 5, 6, 7 and 11. Medical records of children admitted to the SNUCH were reviewed retrospectively.

Results : Adenovirus was isolated from 118(9.0%) of 1,305 children with LRTIs. Serotypes were 3(39.0%), 7(16.9%), 1(11.0%), 2(7.6%), 4(7.6%), 6(5.9%), 11(2.5%), and 5(0.8%) and 10 strains(8.5%) were not neutralized by antisera included in the study. Infections by type 3 and type 7 occurred in outbreaks. Male to female ratio was 1.0:0.9 and mean age was 1.95 years. The clinical diagnoses were pneumonia(83%), acute tracheobronchitis(12%) and bronchiolitis(5%). Associated symptoms, signs and abnormal laboratory findings included cough(100%), sputum(73.5%), fever(54.2%), rale(59.3%), wheezing(34%), anemia(35%) and leukopenia(15.8%). Mortality was in 13.5%. Residual radiologic sequelae was identified in 32.6% of the patients followed.

Conclusion : These data confirms that adenovirus may cause severe lower respiratory tract diseases, and infections by type 3 and 7 may occurred in outbreaks.

Key Words : Adenovirus, LRTIs(lower respiratory tract infection), Serotypes

1) 책임저자: 이환중, 서울의대 소아병원 소아과

Tel : 02)760-3633, Fax : 02)745-4703, E-mail : hoanlee@plaza.snu.ac.kr

가 ,

가 ⁹⁾.

가

2~5%

2~24%

¹⁾,

²⁾.

1, 2, 3, 5 ,

6, 7 .

1, 2, 5

가 , 1995

^{3, 4)},

가

. B

51가

3, 7, 21 E 4

가

(1, 2, 3, 5),

(3, 4, 7, 21), (3, 7),

(8, 19, 37), (11,

21), (2, 3, 5, 40, 41), (1, 2,

4, 5), (7, 12, 32), Reye

(7)

⁵⁾.

DNA

DNA guanine cytosine

A G . A 12, 18,

31 , B 3, 7, 11, 14, 16, 21, 34, 35 , C

1, 2, 5, 6 , E 4 , F 40,

41 , D

⁶⁾.

1.

1998 6 2000 7 2 2

geal aspirate)

1,305

(nasopharyn-

651

가

1, 2, 5, 6

654

가

. 1

⁷⁾,

가 2

1

⁸⁾.

2.

1)

Mucus trap suction catheter

4°C

48

Kruskal-Wallis test, Score test for trend,
Chi-square test .

1.
1,305 118 (9.0%)
가 ,
651 59 (9.0%)
가 . 3~4
가 1
27 . 3 46 (39.0%), 7
20 (17.0%), 1 13 (11.0%), 2 9 (7.6
)%, 4 9 (7.6%), 6 7 (5.9%), 11 3
(2.5%), 5 1 (0.8%) 10 (8.5%)
1, 2, 3, 4, 5, 6, 7, 11 가
.
59 3 18
(30.5%), 7 13 (22.0%), 1 7 (11.9%), 2
6 (10.1%), 4 6 (10.2%), 6 3 (5.0
)%, 5 1 (1.7%), 5
(8.5%) . 4 가 ,
respiratory syncytial virus(RSV) A
2 .
10 , *Mycoplasma pneumo-
niae* 5 , *Bordetella pertussis*
1 , *Streptococcus* 2 , *Enterobacter
cloacae* 2 .

2.

98 6 98 11 51
, 98 12 99 5 27 , 99 6
99 11 25 , 99 12 2000 7
15 . 3 7
. 3 98 10 99 1
98 10 99 12
. 7 98 6 98 11
. 1 99 10

2000 7 (Fig. 1).

3.

가 가 59 2
13 1 11 .
2 6 12 (20.3%), 7
12 14 (23.7%), 13 24
17 (28.8%), 2 5 12 (20.3%), 6
4 (6.8%) .

($P > 0.05$). 가 31 , 가 28

1.0 : 0.9 .
24 40.7% (Table 1).

4.

1)

59
49 (83%),
7 (12%), 3 (5.0%)
, 49 9 (18.4%)
.
2)
38°C 32 (54.2%)
39°C 30
(50.8%) , 38°C

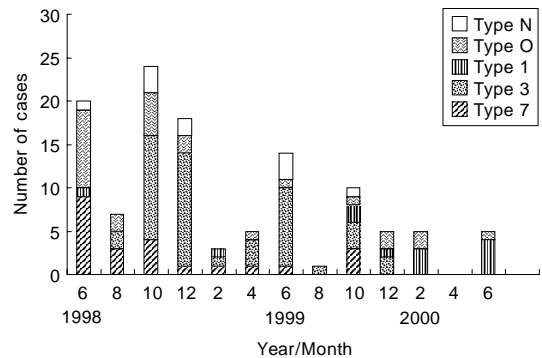


Fig. 1. Distribution of serotypes of adenovirus isolated from children with lower respiratory tract infections. Type O: serotypes 2, 4, 5, 6 and 11, Type N: serotypes not neutralized by antisera 1 through 7 and 11.

8.8 , 23 (39%) ,
 7 ($P>0.05$).
 11 (18.6%)
 ($P>0.05$). , , 23
 35 (59.3%), 20 (34%) (39%) , 가 14
 (23.7%) , 가 가

Table 1. Demographic Data of Children with Lower Respiratory Tract Infections Associated with Adenovirus by Serotypes

Characteristics	Type 1 (n=7)	Type 3 (n=18)	Type 7 (n=13)	Other type* (n=16)	Not-typed† (n=5)	Total (n=59)
Range of age	2 mo~3 yr	3 mo~10 yr	6 mo~6 yr	2 mo~13 yr	4 mo~1.75 yr	2 mo~13 yr
Mean age(yr)	1.13	2.4	1.64	2.33	1.1	1.95
Gender(M : F)	3 : 4	9 : 9	10 : 3	7 : 9	2 : 3	31 : 28
Underlying diseases	4	5	4	8	3	24
Malignancy		2	1	2	2	7
Heart diseases		1	2	3	1	7
Chronic malnutrition	1	1		1		3
Epilepsy	3	1	1	2		7

*Serotypes 2, 4, 5, 6 and 11, † Serotypes not neutralized by antisera 1 through 7 and 11

Table 2. Clinical Characteristics of Children with Lower Respiratory Tract Infections Associated with Adenovirus by Serotypes

Characteristics	Number(%) of cases					Total (n=59)
	Type 1 (n=7)	Type 3 (n=18)	Type 7 (n=13)	Other type* (n=16)	Not-typed* (n=5)	
Clinical diagnosis						
Pneumonia	3(42.8)	16(89.0)	12(92.3)	13(81.3)	5(100)	49(83.0)
Bronchitis	2(28.6)	2(11.0)	1(7.7)	2(12.5)		7(12.0)
Bronchiolitis	2(28.6)			1(6.2)		3(5.0)
Symptoms & signs						
Fever(>38℃)	3(42.0)	7(39.0)	9(69.0)	10(62.5)	3(60)	32(54.2)
Mean duration of fever(day)	7.6	8.9	11.1	7.5	8.8	8.8
Prolonged high fever(>10 days)	2(28.6)	5(27.8)	7(53.8)	5(31.0)	1(20)	20(34.0)
Dyspnea/Tachypnea	1(14.3)	4(22.2)	9(69.0)	6(37.5)	3(60)	23(39.0)
Rale	2(28.6)	10(55.5)	12(92.3)	9(56.3)	2(40)	35(59.3)
Wheeze	2(28.6)	8(44.4)	3(23.0)	6(37.5)	1(20)	20(34.0)
Decreased breathing sound	1(14.3)	5(27.8)	2(15.4)	1(6.2)	1(20)	10(17.0)
Rash	2(28.6)	2(11.0)	1(7.7)	5(31.0)	1(20)	11(18.6)
Vomiting/Diarrhea	1(14.3)	7(39.0)	6(46.0)	5(31.0)	4(80)	23(39.0)
Hepatomegaly	2(28.6)	3(16.7)	6(46.0)	2(12.5)	1(20)	14(23.7)
Seizure	2(28.6)		1(7.7)	4(25.0)		7(11.9)
Mental alteration			3(23.0)			3(5.0)

*Serotypes 2, 4, 5, 6 and 11, † Serotypes not neutralized by antisera 1 through 7 and 11

. 7 (11.9%) (Table 3). 9 (15.2%)
 , 5 , 3 3 , 7
 2 2 , 4 . 5
 (Table 2). , 3 2 7 2
 3) . 1,989.0±422.6 mg/
 dL, 83.6±27.5 mg/dL, LDH 2,451.0±2,020.0
 IU/L, 1,312.0±860.9µL
 (Table 3). 20 (35%) 25.0±23.9% . 5
 10 g/dL , 5,000/mm³ ,
 9 (15.8%), 20,000/mm³ 3 2 3 7 가
 가 1 (1.8%) .
 , 100,000/mm³ 7 (12.3%), 4)
 50,000/mm³ 2 (3.5%) 59
 . CRP 55 10 mg/L , 12 (20.3%) .
 4 (7.3%) . ALT 가 25 (43.9%), 39 (66.1%)
 AST 가 14 (24.5%) , 가 , 24 (40.7%)
 16 PT 6 (37.5%), aPTT , 5 (8.5%) 가 ,
 3 (18.8%) 가 , FDP 7 (43.7%) 9 (15.2%) .

Table 3. Laboratory Findings of Children with Lower Respiratory Tract Infections Associated with Adenovirus by Serotypes

Laboratory findings	Type 1 (n=6)	Type 3 (n=18)	Type 7 (n=13)	Other type* (n=15)	Not-typed† (n=5)	Total(%) (n=57)
CBC						
Anemia(Hb <10 g/dL)	2	6	4	5	3	20(35.0)
Leukopenia(WBC <5,000/µL)	0	4	2	1	2	9(15.8)
Leukocytosis(WBC >20,000/µL)	1	0	0	0	0	1(1.8)
Thrombocytopenia(Platelet <100,000/µL)	0	2	3	2	0	7(12.3)
CRP						
≥0.1 mg/dL	2	13	11	14	3	43(78.2)
≥10 mg/dL	0	1	2	1	0	4(7.3)
Liver enzymes						
ALT >60 IU/L	4	5	7	4	2	22(38.6)
>300 IU/L	1	0	2	0	0	3(5.3)
AST >60 IU/L	3	2	3	4	2	12(21.0)
>300 IU/L	0	0	1	1	0	2(3.5)
Coagulation test[‡]						
Prolonged PT	0	0	3	3	0	6(37.5)
aPTT ≥40 sec	0	0	2	1	0	3(18.8)
Positive FDP	0	1	5	1	0	7(43.7)
Proteinuria	0	1	1	1	0	3(5.2)
Hematuria	0	1	1	1	0	3(5.2)

* Serotypes 2, 4, 5, 6 and 11, † Serotypes not neutralized by antisera 1 through 7 and 11, ‡n=16

Table 4. Treatment and Outcomes of Children with Lower Respiratory Tract Infections Associated with Adenovirus by Serotypes

	Number(%) of cases					Total (n=59)
	Type 1 (n=7)	Type 3 (n=18)	Type 7 (n=13)	Other type* (n=16)	Not-typed* (n=5)	
Mean duration of hospitalization	9.1	9.7	14.4	19.1	9.8	10.2
Oxygen inhalation	1(14.3)	6(33.0)	9(69.2)	5(31.0)	3(60)	24(40.7)
Mechanical ventilation	0	2(11.0)	4(30.8)	2(12.5)	1(20)	9(15.2)
Use of IVIG	0	1(5.5)	4(30.8)	2(12.5)	1(20)	8(13.5)
Fetal cases		1(5.5)	3(23.0)	3(16.0)	1(20)	8(13.5)
By adenoviral infection	0	1(5.5)	2(15.4)	0	0	3(5.0)
By underlying disease	0	0	1(7.7)	3(18.7)	1(20)	5(8.5)

*Serotypes 2, 4, 5, 6 and 11, * Serotypes not neutralized by antisera 1 through 7 and 11

5) 천 , , 가 .
15
,
24 (32.6%) 5 (32.6%), 3
(40.7%), (20%) , 8
9 3 , 3 ,
(15.2%) . 9 1 가 (Table 5).
3 2 , 7 4 ,
2 , 1
10.2 2~5%
20 1 8% 20%
1 25 가 1, 2).
8 (13.5%)
가 가 5 (5%),
3 3 1 , 7 2 11, 12).
9%
(Table 4). 가 7 1 7
가 ,
1 가 , 1 가 , 1 가 6 5
, 1 가 3~18
. 90%
6)
46 (78%) 가 가
7.0 (1~22) , 가 ,
6
15 (32.6%) , , 가

Table 5. Results of Clinical Follow Up in Children with Lower Respiratory Tract Infections Associated with Adenovirus by Serotypes

Characteristics	Number(%) of cases					Total (n=59)
	Type 1 (n=7)	Type 3 (n=18)	Type 7 (n=13)	Other type* (n=16)	Non-typed* (n=5)	
Patients followed	5	14	9	16	2	46
Mean F/U duration(months)	2.0	7.5	7.2	7.7	6.5	7.0
Persistent respiratory symptoms	2(40.0)	5(35.7)	2(22.2)	5(31.2)	1(50)	15(32.6)
Persistent abnormal radiographic findings	2(28.6)	6(42.9)	2(15.4)	3(18.7)	2(40)	15(32.6)
Infiltration		1	1	1	2	5(33%)
Hyperaeration		2		1		3(20%)
Bronchiectasis		2		1		3(20%)
Bronchiolitis obliterans	1	1	1			3(20%)
Pleural thickening	1					1(6.7%)

F/U : Follow up(during 1~22 months), *Serotypes 2, 4, 5, 6 and 11, † Serotypes not neutralized by antisera 1 through 7 and 11

, , (1.4%), 2
(0.5%), (0.1%)
13). 6 14 (0.9%)
% 1 가 44 ~ 50% 가 1990 11
1 2 1994 4 가
가 . 5 가 70 ~ 80%가 가 16), 1996 5
1, 2 , 7 7
50%가 5 14). 4, 17, 27).
1%가 1983 WHO ,
1967 1976 25,000
4% 6). 2, 1, 7, 3, 5, 6, 4, 8 .
1 11 5 3, 4, 8, 7, 19 ,
가 93.2% C , 3
가 . 8~9 , 7 8 . A
가 , C ,
가 15). 3 7
B C , 4 19
가 .
10) 1990 11 1994 4
 , 45.9% 가 1982 1993
, RSV(27.2%), 3 (7.8 40% 가
(3.9%), A (3.9%), , 3, 2, 1, 5
(3.9%), 1 (1.7%), B . 9.5%

190 : 9 2 2002

3, 2, 1, 5 . 20%
3, 4, 8, 37, 19 가
. 7 (0.2%) ,
¹⁸⁾ 1996 11 1997
1 7 가
¹⁹⁾ . 8.8
1958 1990 33 1976
1990 15 , CRP
Korppi ²⁵⁾ .
1976 1980 7 , 1981 55%
1990 3 ²⁰⁾ .
25%, 45% .
hex-
on fiber 가 (30%) .
4 , 5
penton base fiber 가 가 (35.7%).
rhesus monkey X
25%
²⁶⁾ .
⁶⁾ hexon ,
59.3% 34%
66.1%
3 가 (40.7%)
(8.4%)가
^{21, 22)} 3, 15.2%
4, 8 5 가
1,989 mg/dL, 84 mg/dL, LDH 2,451 U/L,
1,312 μL 12.8%,
²³⁾ 25% , LDH 가
1~7,
11 가 .
3
Ruuskanen ²⁴⁾ 105 2 가
(>39.4°C)
(5.4) ,
 ,

. Type 7a
 type 7a 가가
 가²⁷⁾, ribavirin
²⁸⁾,
 ganciclovir
 ribavirin 가
²⁹⁾.
 가 3 7
 , 6 5
 , 가 ,
 가
 :
 : 1998 6 2000 7
 . HEP-2
 ,
 1, 2, 3, 4, 5, 6, 7, 11
 .
 : 1,305 118 (9.0
 %) , 3 46 (39%),
 7 20 (16.9%), 1 13 (11.0%), 2 9 (7.6
 %), 4 9 (7.6%), 6 7 (5.9%), 11 3 (2.5%),
 5 1 (0.8%), 10 (8.5%)가
 . 3 1998 10 1999 12
 7 1998 6 11
 . 1.0 : 0.9
 1.95 . 49 (83%),

- 7 (12%), 3
 (5.0%) . ,
 (100%), 가 (73.5%), (54.2%), (59.3%),
 (34%), (35%), (15.8%) .
 13.5% ,
 46 15 (32.6%)
 .
 :
 ,
 1) Brandt CD, Kim HW, Vargosko AJ, et al. In-
 fections in 18,000 infants and children in a
 controlled study of respiratory tract disease, I.
 Adenovirus pathogenicity in relation to serologic
 type and illness syndrome. Am J Epidemiol
 1969;70:484-500.
 2) Claesson BA, Trollfors B, Brolin I, et al. Etiol-
 ogy of community-acquired pneumonia in chil-
 dren based on antibody responses to bacterial
 and viral antigens. Pediatr Infect Dis J 1989;8:
 856-62.
 3) , , . 1996
 Adenovirus . 1996;3:
 145-53.
 4) , , .
 .
 1998;41:1070-8.
 5) Edwards KM, Thompson J, Paolini J, Wright
 PF. Adenovirus infections in young children.
 Pediatrics 1985;76:420-4.
 6) Baum SG. Adenovirus. In : Mandell GL, Bennett
 JE, Dolin R. Principles and practice of infectious
 disease. 5th ed. New York : Churchill Livingstone,
 2000:1624-9.
 7) Fox JP, Brandt CD, Wassermann FE, et al. The
 Virus Watch Program : a continuing surveillance
 of viral infections in metropolitan New York
 families. VI. Observations of adenovirus
 infections : virus excretion patterns, antibody re-

- sponse, efficiency of surveillance, patterns of infections and relation of illness. *Am J Epidemiol* 1969;89:25-50.
- 8) Foy HM, Cooney MK, Hatlen JB. Adenovirus type 3 epidemic associated with intermittent chlorination of a swimming pool. *Arch Environ Health* 1968;17:795-802.
 - 9) , , .
1996;3:154-61.
 - 10) Yun BY, Kim MR, Park JY, Choi EH, Lee HJ, Yun CK. Viral etiology and epidemiology of acute lower respiratory tract infections in Korean children. *Pediatr Infect Dis J* 1995;14:1054-9.
 - 11) Zahradnik JM, Spencer MJ, Porter DD. Adenovirus infection in the immunocompromised patient. *Am J Med* 1980;68:725-32.
 - 12) Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. *Clin Infect Dis* 1998;27:1194-200.
 - 13) Abzug MJ, Levin MJ. Neonatal adenovirus infection: four patients and review of the literature. *Pediatrics* 1991;87:890-6.
 - 14) D'ambrosio E, del Grosso N, Chicca A, Miodulla M. Neutralizing antibodies against 33 human adenoviruses in normal children in Rome. *J Hyg Camb* 1982;89:155-61.
 - 15) Schmitz H, Wigand R, Heinrich W. Worldwide epidemiology of human adenovirus infections. *Am J Epidemiol* 1983;117:455-66.
 - 16) , , , , .
1996;39:1690-9.
 - 17) , , . 1995
1996;39:1247-53.
 - 18) Yamadera S, Yamashita K, Akatsuka M, et al. Adenovirus surveillance, 1982~ 1993, Japan: A report of the national epidemiological surveillance of Infectious agents in Japan. *Jpn J Med Sci Biol* 1995;48:199-210.
 - 19) Sakata H, Taketazu G, Hagaya K, et al. Outbreak of severe infection due to adenovirus type 7 in a paediatric ward in Japan. *J Hosp Infect* 1998;39:207-11.
 - 20) Li QG, Zheng QJ, Liu YM, Wadell G. Molecular epidemiology of adenovirus type 3 and 7 isolated from children with pneumonia in Beijing. *J Med Virol* 1996;49:170-7.
 - 21) Takeuchi S, Itoh N, Uchio E, Aoki K, Ohno S. Serotyping of adenoviruses on conjunctival scrapings by PCR and sequence analysis. *J Clin Microbiol* 1999;37:1839-45.
 - 22) Akalu A, Seidel W, Liebermann H, Bauer U, Dohner L. Rapid identification of subgenera of human adenovirus by serological and PCR assays. *J Virol Methods* 1998;71:187-96.
 - 23) Wood SR, Sharp IR, Caul EO, et al. Rapid detection and serotyping of adenovirus by direct immunofluorescence. *J Med Virol* 1997;51:198-201.
 - 24) Ruuskanen O, Meurman O, Sarkkinen H. Adenoviral diseases in children: A study of 105 hospital cases. *Pediatrics* 1985;76:79-83.
 - 25) Korppi M, Leinonen M, Makela PH, Launiala K. Mixed infection is common in children with respiratory adenovirus infection. *Acta Paediatr Scand* 1991;80:413-7.
 - 26) Wildin SR, Chonmaitree T, Swischuk LE. Roentgenographic features of common pediatric viral respiratory tract infections. *Am J Dis Child* 1988;142:43-6.
 - 27) Hong JY, Lee HJ, Piedra PA, et al. Adenovirus lower respiratory tract infections in hospitalized Korean children: epidemiology, clinical features, and prognosis. *Clin Infect Dis* 2001;32:1423-9.
 - 28) Shetty AK, Gans HA, So S, Millan MT, Arvin AM, Gutierrez KM. Intravenous ribavirin therapy for adenovirus pneumonia. *Pediatr Pulmonol* 2000;29:69-73.
 - 29) Murphy GF, Wood DP Jr, McRoberts JW, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. *J Urol* 1993;149:565-6.