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ORIGINAL ARTICLE

Risk factor analysis and molecular epidemiology of respiratory adenovirus infections among children in northern Taiwan, 2009–2013

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Abstract *Background/Purpose:* Respiratory infections caused by human adenoviruses (HAdV) are worldwide, and have significantly increased recently in Taiwan. This study aimed to clarify the molecular epidemiology and risk factors of HAdV severe infections and pneumonia among Taiwanese children.
Methods: Patients with HAdV infections and hospitalized in a medical center between 2009 and 2013 were divided into severe or nonsevere HAdV infections based on whether or not they received intensive care. HAdV pneumonia was identified for comparison. The HAdV genotype was determined by sequencing the partial hexon and fiber genes. The nucleotide sequences were compared by phylogenetic analysis.
Results: The 176 patients (97 boys, 79 girls) had a median age of 3.7 years. The HAdV infections circulated year-round. HAdV B3 (54.5%) was the most common genotype, followed by HAdV C2

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(21%), HAdV E4 (8%), and HAdV B7 (6.8%). Thirty-two patients needed intensive care. In multivariate analysis, the risk factors for severe HAdV infections were underlying neurologic diseases [odds ratio (OR): 164.9; $p < 0.001$], prematurity (OR: 10.9; $p = 0.042$), and HAdV B7 (OR: 39.5; $p = 0.011$). Twenty-nine patients had HAdV pneumonia. Patients with underlying neurologic diseases (OR 76.8; $p < 0.001$), airway anomaly (OR 15.1; $p = 0.033$), chronic lung diseases (OR 12.5; $p = 0.047$), weight $< 3^{rd}$ percentile (OR 5.5; $p = 0.027$), and HAdV B7 (OR 4.2; $p = 0.002$) had higher incidences of pneumonia. Four with underlying neurologic diseases died of acute respiratory distress syndrome.

Conclusion: HAdV infections circulate all year-round. HAdV B7 is strongly related to severe infections and pneumonia. Underlying neurologic diseases and prematurity are risk factors for severe HAdV infections.

Introduction

Human adenoviruses (HAdV) are nonenveloped DNA viruses and are common causative pathogens of acute respiratory infections. In the past few years, there has been a significant increase in the incidence of HAdV infections in Taiwan.[1,2] It may cause a wide variety of clinical manifestations, from the common cold, tonsillitis, pharyngoconjunctival fever, acute otitis media, and gastroenteritis, to life-threatening pneumonia, myocarditis, and meningoencephalitis.[3–5] Some studies have reported an association between HAdV in childhood and outcomes.

The HAdV serotypes and characteristics of children have been shown to play an important role in outcome. Children aged 1–2 years are at higher risk of lower respiratory tract infections than those of other age groups.[6] Life-threatening HAdV infections are reported in younger children, immunocompromised patients, those with underlying chronic diseases, and previously healthy children.[7–9] Greater knowledge about differences in virulence and organ tropism among the HAdV serotypes increase the medical value of HAdV classification.[10]

In general, HAdV species B, C, and E (HAdV-B, -C, and -E) cause respiratory infections. They are distributed globally and occur throughout the year, crossing all age groups. HAdV-B3 has been common in Taiwan in the previous years.[11] A prior report shows that HAdV serotype 3 causes the most HAdV infections in the autumn and winter of 1999–2000.[12] Certain serotypes are associated with particular clinical features and severe illness and HAdV serotypes 3, 5, 7, and 21 have caused death after severe infections. Among these serotypes, serotypes 3 and 7 have a higher risk of causing severe respiratory illness.[1,8,13,14]

However, studies on risk factors of severe HAdV infections and molecular epidemiology of HAdV are limited in Taiwan. The aim of this study was to determine the molecular epidemiology of HAdV, its clinical presentations, and the risk factors of severe HAdV infections among Taiwanese children.

Methods

Ethics statement

The Ethics Committee of MacKay Memorial Hospital, Taipei, Taiwan, R.O.C. approved the study protocol (Institutional Review Board number 14MMHIS 162).

Patient inclusion

This study enrolled 176 children aged 18 years or younger with positive HAdV cultures and admitted to the Pediatric Department of MacKay Memorial Hospital, a tertiary medical center, between January 2009 and December 2013. The medical charts were reviewed and the demographic data, clinical features, laboratory results, chest X-ray, underlying diseases, clinical diagnosis, and outcomes were analyzed.

Viral culture and adenovirus genotyping

Virus cultures were performed via throat swabs with sterile cotton buds and nasopharyngeal aspirates (NPA) from all participants within 48 hours of admission. The specimens were preserved in standard transport media under refrigeration and transported to the Department of Clinical Virology and Microbiology Laboratory of MacKay Memorial Hospital for virus culture.[15] The viral stocks consisted of only supernatant and stored at −80°C immediately after harvest until use.

Nucleic acid extraction was performed using a High Pure Viral Nucleic Acid kit (Roche, Basel, Switzerland) according to the manufacturers' instructions. Partial hexon gene was amplified by polymerase chain reaction (PCR), which was set according to a previous study.[16]

The PCR assay was conducted using the SapphireAmp Fast PCR Master Mix (TaKaRa Inc., Shiga, Japan). Amplification was performed in a GeneAmp PCR System 9700 thermocycler (Applied Biosystems Inc., Carlsbad, CA, USA) with the following parameters: 94°C for 1 minute followed by 40 cycles of 20 seconds at 98°C, 30 seconds at 60°C, 1

minute at 72°C, and 7 minutes of extension at 72°C. For nucleotide sequence analysis of the fiber gene, the PCR was performed at 94°C for 1 minute followed by 40 cycles of 98°C for 20 seconds, 55°C for 30 seconds, 72°C for 60 seconds, a final extension at 72°C for 7 minutes, and then held at 4°C. A multiplex PCR was used to target the HAdV fiber gene. The fiber gene PCR generated species-specific product sizes, as described previously.[17]

Sequencing and phylogenetic analysis

The PCR products were sequenced using the BigDye 3.1 Terminator cycle sequencing reagents on an ABI Prism 3730 DNA Analyzer (Applied Biosystems, Forest City, CA, USA). Phylogenetic trees were reconstructed by maximum likelihood (ML) methods for the partial hexon and fiber genes using the MEGA 5 software package.[18] The reliability of the tree topology was statistically evaluated by bootstrap analysis with 1000 replications. To reduce calculation time, only one sequence was maintained in phylogenetic analysis, whereas multiplex studied the HAdV strains with identical sequence and collection year.

Definitions

Patients with severe respiratory illness requiring intensive care, inotropic agents, and mechanical ventilator support were transferred to the pediatric intensive care unit (PICU) and were classified as severe HAdV infections. Fever was defined as a body temperature of >38°C. The duration of fever before hospitalization was provided by the caregivers, whereas the duration of fever after hospitalization was collected from medical records.

Epilepsy, cerebral palsy, central nervous system anomalies, and encephalopathy were grouped as underlying neurologic diseases. Vocal cord palsy, trachea stenosis, and laryngomalacia were identified as airway anomalies. A radiologist and a pediatrician interpreted all chest X-ray films. Patients were classified as having pneumonia if the chest X-rays showed evidence of patchy consolidation. A body weight <3rd percentile was defined as underweight. The percentile of weight was measured according to the growth charts for Taiwanese children and adolescents based on the World Health Organization standards and health-related physical fitness.

Statistical analysis

The significance of risk factors that were possibly associated with severe HAdV infections and pneumonia were assessed. The risk factors included sex, age, underlying diseases, laboratory data, and genotypes of HAdV. The proportional variables were compared by Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared by Student *t* test or the Mann–Whitney *U* test. A multivariate logistic regression analysis was used for adjusted confounding variables simultaneously and for the multivariate-adjusted odds ratios (OR). Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical features

For the study period (2009–2013), 176 patients were hospitalized for HAdV infections, including 97 boys and 79 girls. Their median age was 3.8 years (inter-quartile range, 1.2–5.4 years), with 2–5 years as the predominant age group (44.3%). During the acute stage of the infections, 32 patients (18.2%) were admitted to the PICU, including four patients (2.3%) who eventually died. Overall, 27.3% of patients had underlying diseases or conditions such as prematurity (8%), underlying neurologic diseases (6.3%), asthma (5.1%), chronic lung diseases (5.1%), congenital heart diseases (4.5%), and airway anomalies (3.9%). Their clinical features and laboratory results are summarized in Tables 1 and 2.

The HAdV genotypes were classified as 96 strains of HAdV B3 (54.5%), 37 HAdV C2 (21%), 14 HAdV E4 (8%), 12 HAdV B7 (6.8%), eight HAdV C5 (4.5%), two HAdV C6 (1.1%), one HAdV57 (0.6%), four mixed genotype (2.3%), and two untyped (1.1%). The HAdV B3 was the most frequently encountered genotype. Phylogenetic analysis of HAdV hexon and fiber genes (Figures 1A and 1B) demonstrated that the isolation were well supported in both hexon and fiber tree for all known genotypes except the HAdV6 and

Table 1 Demographics and characteristics of patients hospitalized due to adenovirus infections ($n = 176$).

Characteristics	No. (%)
Mean age (y)	3.88 ± 2.56
Age group (y)	
<1	18 (10.2)
≥1–2	29 (16.5)
≥2–5	78 (44.3)
≥5	51 (29.0)
Sex	
Female	79 (44.9)
Male	97 (55.1)
Body weight	
<3rd percentile	15 (8.5)
>97th percentile	11 (6.3)
Underlying diseases	
Prematurity	14 (8.0)
Neurological diseases	11 (6.3)
Chronic lung diseases	9 (5.1)
Asthma	9 (5.1)
Congenital heart diseases	8 (4.5)
Airway anomalies	7 (3.9)
Diagnosis	
Acute tonsillitis/pharyngitis	126 (71.6)
Acute bronchiolitis/bronchitis	81 (46.0)
Pneumonia	29 (16.5)
Acute Respiratory Distress Syndrome	10 (5.7)
Croup	1 (0.6)
Severe infection	
Requiring intensive care	32 (18.2)
Mortality	4 (2.3)

Table 2 Fever, hospital duration, and laboratory results of patients hospitalized due to adenovirus infections ($n = 176$).

Characteristics	Pneumonia ($N = 29$)	Nonpneumonia ($N = 147$)	p	ICU cases ($N = 32$)	Non-ICU cases ($N = 144$)	p
Fever						
Mean duration (d)	10.4 ± 5.9	5.5 ± 2.2	<0.001	8.2 ± 6.7	5.9 ± 2.3	0.060
Before admission (d)	2.8 ± 2.8	3.5 ± 2.1	0.200	1.8 ± 2.3	3.7 ± 2.0	<0.001
During hospitalization (d)	7.6 ± 6.0	2.0 ± 1.3	<0.001	6.3 ± 6.3	2.2 ± 1.5	0.001
Duration of hospitalization	22.6 ± 20.9	4.7 ± 3.2	<0.001	21.1 ± 20.6	4.6 ± 2.8	<0.001
Laboratory results						
Hb (g/dL)	11.3 ± 1.9	11.8 ± 1.1	0.199	11.1 ± 1.8	11.8 ± 1.1	0.048
Platelet ($\times 10^3$/uL)	262.5 ± 160.0	266.8 ± 79.2	0.888	261.6 ± 150.2	267.1 ± 80.8	0.841
WBC ($\times 10^3$/uL)	11.5 ± 4.9	13.2 ± 5.4	0.098	12.2 ± 5.4	13.1 ± 5.4	0.401
CRP (mg/dL)	9.3 ± 10.2	6.0 ± 5.1	0.091	8.0 ± 10.2	6.2 ± 5.0	0.324
Band (%)	6.5 ± 9.0	1.0 ± 1.9	0.003	5.7 ± 8.8	1.0 ± 2.1	0.005

Data are presented as mean ± standard deviation.
CRP = C-reactive protein; Hb = hemoglobin; ICU = intensive care unit; WBC = white blood cell count.

HAdV57, which were indistinguishable in the fiber tree but fully resolved in the hexon tree. The HAdV infections circulated year-round, with a tendency to be most common in September (16%), followed by December (10.7%) and July (10.2%; Figure 2).

Clinical and viral characteristics of severe adenovirus infections

In this study, 32 patients (18.2%) with HAdV infections required intensive care due to respiratory failure (87.5%), intractable seizure with cyanosis (9.4%), tachycardia (3.6%), and hypotension (3.6%). Their median age was 1.9 years (inter-quartile range, 1.0—4.3 years). The average length of hospital stay was 21.1 ± 20.6 days, which was significantly longer than that of patients with nonsevere infection (Table 2).

Among the patients with severe HAdV infections, 23 (71.9%) had pneumonia and 10 (34.4%) had acute respiratory distress syndrome (ARDS). Twelve patients were intubated, seven patients required noninvasive mechanical ventilation, and 11 patients needed oxygen supplement for respiratory support. Four patients (12.5%) died.

Those who were underweight ($p = 0.001$) or premature ($p = 0.005$), or had underlying neurologic diseases ($p < 0.001$), chronic lung diseases ($p < 0.001$), airway anomalies ($p < 0.001$), or congenital heart disease ($p = 0.037$) exhibited a higher incidence of severe HAdV infections (Table 3). Moreover, conditions such as higher band cell count ($p < 0.001$), shorter fever duration prior to admission ($p < 0.001$), longer fever duration during hospitalization ($p = 0.001$), and longer hospital stay ($p < 0.001$) were associated with severe HAdV infections.

Although HAdV-B3 was the most common serotype, there was a relation between HAdV-B7 and severe HAdV infections ($p = 0.045$). After adjusting for covariates by multivariate analysis, severe HAdV infections were associated with underlying diseases, especially underlying neurologic diseases [OR: 164.9, 95% confidence interval (CI): 9.1—2998.8; $p < 0.001$], prematurity (OR: 10.9, 95% CI: 1.1—108.1; $p = 0.042$), and serotype B7 infection (OR: 39.5, 95% CI: 2.3—672.1; $p = 0.011$).

Characteristics of pneumonia from adenovirus infections

Twenty-nine patients had pneumonia and 23 patients (79.3%) required intensive care during the acute stage of infections. Their median age was 3.5 years (interquartile range, 1.5—6.2 years). Among the patients with pneumonia, 21 had multilobar pneumonia and eight had single lobar pneumonia. After analyzing the risk factors for pneumonia (Table 4), most patients had chronic underlying diseases, particularly neurological diseases. Four patients with underlying neurologic diseases died because of HAdV pneumonia with ARDS. Three patients were infected by HAdV-B3 (75%) and one patient was infected by HAdV-C5 (25%).

Compared to patients who did not have pneumonia, those with HAdV pneumonia had significant characteristics: weight <3rd percentile ($p = 0.004$), underlying neurologic diseases ($p < 0.001$), airway anomalies ($p = 0.001$), and chronic lung diseases ($p = 0.001$). Patients with HAdV pneumonia also had significantly higher band cell count ($p = 0.003$). However, the white blood cell count and C-reactive protein (CRP) were not significantly different.

HAdV B7 ($p = 0.030$) was statistically significantly related to HAdV pneumonia, longer fever duration ($p < 0.001$), and longer hospital stays ($p < 0.001$). By multivariate logistic regression of risk factors for HAdV pneumonia, underlying neurologic diseases (OR: 76.8, 95% CI: 9.3—634.1; $p < 0.001$), airway anomalies (OR: 15.1, 95% CI: 2.8—82.3; $p = 0.033$), chronic lung diseases (OR: 12.5, 95% CI: 2.9—53.6; $p = 0.047$), and weight <3rd percentile (OR: 5.5, 95% CI: 1.8—16.7; $p = 0.027$) were predictive factors for pneumonia. Patients infected by HAdV-B7 (OR: 4.2, 95% CI: 1.2—14.2; $p = 0.002$) also were at higher risk for the development of HAdV pneumonia.

Discussion

Previous studies from Taiwan have demonstrated that HAdV B3 as the main serotype circulating for the past 10 years. Outbreaks of HAdV in 2004—2005 and 2011 caused by HAdV

A.

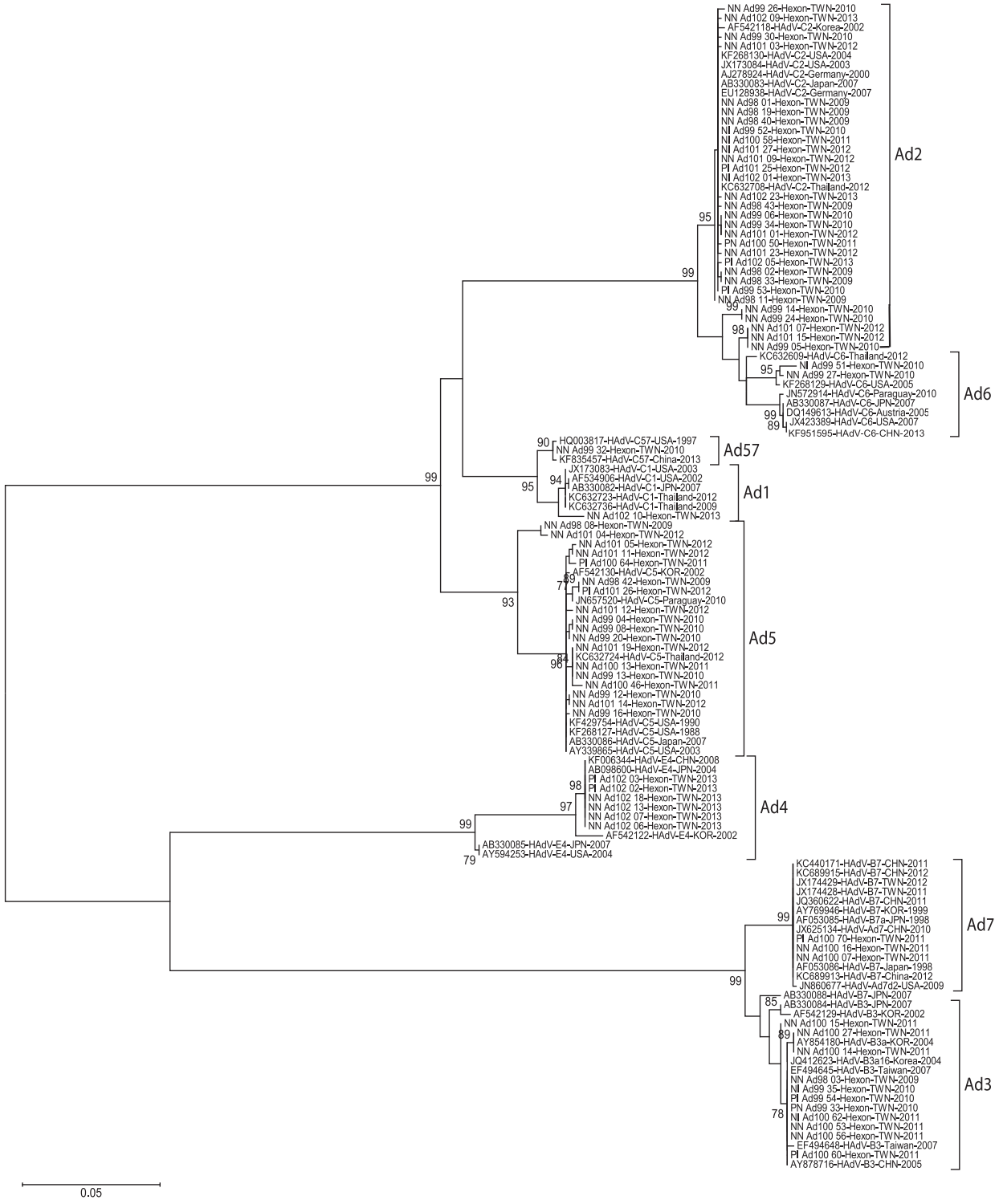

Figure 1. Phylogenetic analysis of adenovirus hexon and fiber genes. The bootstrap value of trees was shown next to reliable (>75%) branches. The scale bar represented the branch lengths measured in the number of substitutions per site. (A) Hexon gene. (B) Fiber gene.

B.

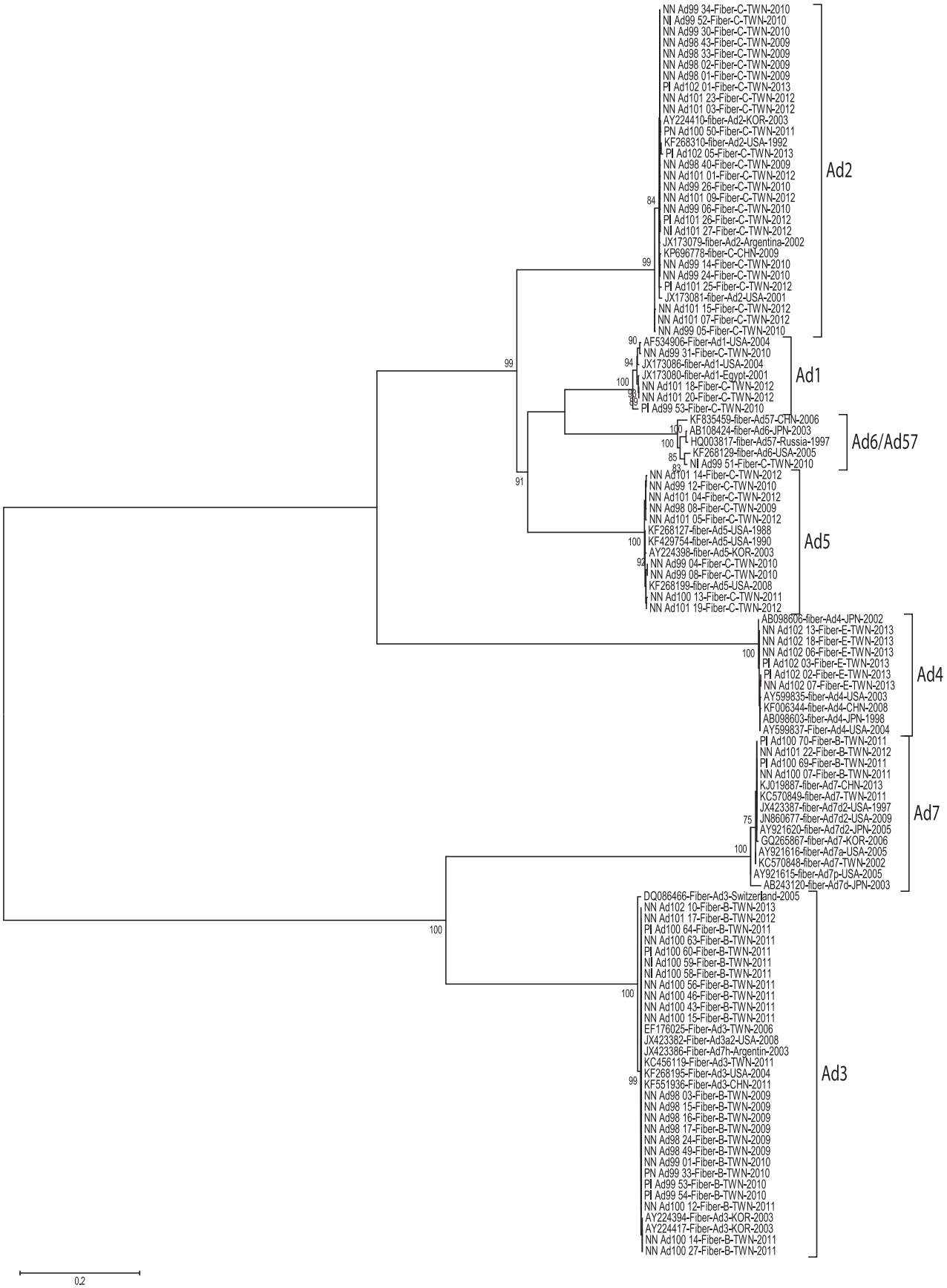

Figure 1. (*continued*).

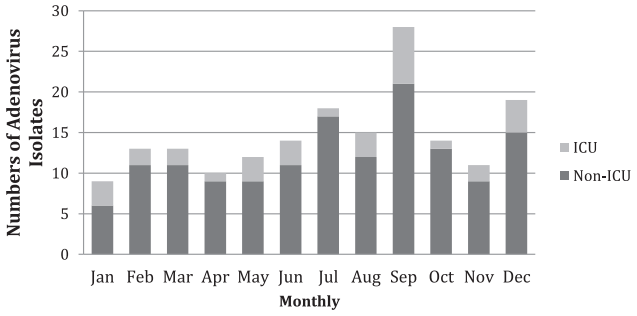

Figure 2. Monthly distribution of adenovirus isolated from the intensive care unit (ICU) and non-ICU between 2009 and 2013.

B3 have been reported.[1,19] The prevalence of HAdV B7 had increased in 2011.[2] HAdV B3 and B7 can contribute to an epidemic and cause severe HAdV infections and high mortality. Furthermore, HAdV B7 is also associated with pneumonia.[1,14,20] In our study, the HAdV outbreak in 2011 is mainly caused by both HAdV B3 (77.0%) and B7 (16.4%) and involved 15 children infected with HAdV B3 and three children infected with HAdV B7. All were admitted to the PICU and two patients eventually died.

HAdV infections occur annually and spread throughout the year in Taiwan, but the epidemiology changes each year. Cheng et al[21] have shown a significant increase in HAdV B3 incidence from November 2004 to January 2005, with a seasonal variation. The HAdV serotype 3 occurring more often during autumn and winter has been reported between 1999 and 2000.[12] The peak incidence of HAdV B3 in this study is from September to December, which is similar to findings of a previous study.[12] However, there is no significant seasonal variation in this 5-year longitudinal study.

The HAdV infections may occur at any age although most occur in children younger than 5 years.[22,23] This study revealed that the majority of HAdV infections occurred in ages 2—5 years, with the youngest at 11 days old and the oldest was 14.6 years old. Ten patients were younger than 6 months old. Among them, seven infants had underlying diseases and were admitted to the PICU due to respiratory distress with subsequent multiple lobar pneumonia. The findings suggest that infants younger than 6 months old, especially those with chronic underlying diseases, may have severe HAdV pneumonia.

Patients with severe HAdV infections and pneumonia have prolonged fever and require longer hospitalization. They have shorter fever duration prior to admission but longer fever duration in hospitalization, indicating that patients with severe illness will progress rapidly and should be hospitalized earlier for management.

Prematurity and congenital heart diseases do not show statistical significance for HAdV pneumonia, but they are significantly associated with disease severity. Underlying neurological diseases, chronic lung diseases, and airway anomalies are all significantly more in severe adenoviral infection and pneumonia. Tsou et al[2] have found that patients with underlying conditions, especially neurologic diseases, are more likely to experience HAdV infections.[2] Bedridden children or those with neuromuscular dysfunction have decreased pulmonary capacity. Their respiratory muscle weakness and poor coordination make them vulnerable to pneumonia.[24] Children with airway anomalies or chronic lung diseases are more likely to experience impaired pulmonary function and respiratory structure. It is reasonable to speculate that these children have ineffective cough and poor airway clearance, thereby increasing their risk of developing severe HAdV pneumonia.

Table 3 Analysis of risk factors for severe adenovirus infections.

Characteristic	ICU cases (n = 32)	Non-ICU cases (n = 144)	Univariate p
Mean age (y)	3.4 ± 3.7	4.0 ± 2.3	0.417
Male sex	17 (53.1)	81 (56.2)	0.845
Body weight			
<3rd percentile	8 (25.0)	7 (4.9)	0.001
>97th percentile	4 (12.5)	7 (4.9)	0.116
Underlying diseases			
Airway anomalies	7 (21.9)	0 (0.0)	<0.001
Neurological diseases	10 (31.2)	1 (0.7)	<0.001
Chronic lung diseases	9 (28.1)	0 (0.0)	<0.001
Prematurity	7 (21.9)	7 (4.9)	0.005
Congenital heart diseases	4 (12.5)	4 (2.8)	0.037
Genotypes			
B3	15 (46.9)	81 (56.2)	0.433
B7	5 (15.6)	7 (4.9)	0.045
C2	6 (18.8)	31 (21.5)	0.815
E4	2 (6.2)	12 (8.3)	1.000
Pneumonia	23 (71.9)	6 (4.2)	<0.001
ARDS	11 (34.4)	0 (0.0)	<0.001
Death	4 (12.5)	0 (0.0)	0.001

Data are presented as n (%) or mean ± standard deviation.
ARDS = acute respiratory distress syndrome; ICU = intensive care unit.

Table 4 Analysis of risk factors for pneumonia caused by adenovirus infections.

Characteristic	Pneumonia (n = 29)	Nonpneumonia (n = 147)	Univariate p
Mean age (y)	4.3 ± 3.7	3.8 ± 2.3	0.526
Male sex	14 (48.3)	84 (57.1)	0.418
Body weight			
<3rd percentile	7 (24.1)	8 (5.4)	0.004
>97th percentile	4 (13.8)	7 (4.8)	0.086
Underlying diseases			
Airway anomalies	15 (17.2)	2 (1.4)	0.001
Neurological diseases	10 (34.5)	1 (0.7)	<0.001
Chronic lung diseases	6 (20.7)	3 (2.0)	0.001
Prematurity	5 (17.2)	9 (6.1)	0.058
Congenital heart diseases	2 (6.9)	6 (4.1)	0.620
Genotypes			
B3	16 (55.2)	80 (54.4)	1.000
B7	5 (17.2)	7 (4.8)	0.030
C2	5 (17.2)	32 (21.8)	0.803
E4	2 (6.9)	12 (8.2)	1.000
Admitted ICU	23 (79.3)	9 (6.1)	<0.001
Death	4 (13.8)	0 (0)	0.001

Data are presented as n (%) or mean ± standard deviation.
ICU = intensive care unit.

However, underweight is associated with HAdV pneumonia in the children in this study. This finding has not been previously reported. Nutrition is an important element for the immune system. Consequently, long periods of poor nutrition may lead to immunologic deficit. In this study, most underweight patients also have chronic underlying diseases, particularly neurologic diseases. This results in feeding limitation and in some cases, enteral feeding. Thus, total daily energy intake is insufficient. Underweight patients with chronic underlying diseases may have weaker immune response to severe infections, leading to a higher rate of HAdV pneumonia.

Leukopenia, lower hemoglobin levels, and thrombocytopenia have been reported in severe HAdV infections, but this study has found no such correlation.[2] Differences may be attributed to specimen collection time and research designs. Nonetheless, band cell as a measure of inflammation is significantly higher in severe HAdV infections or pneumonia, which has not been reported before.

In this study, both the severe HAdV and the pneumonia groups show higher C-reactive protein (CRP) levels but no significant difference when compared to non-pneumonia and nonsevere infection groups. Therefore, if a patient has higher band cell counts and higher CRP level, not only bacterial infection but also severe viral infection such as adenovirus infection should be considered. In this case, adenoviral antigen rapid test can be performed if the clinical presentation and laboratory data are highly suspect.

In conclusion, this study demonstrates that patients who present with underlying neurologic diseases, chronic lung diseases, and malnutrition have higher incidences of HAdV pneumonia and require earlier hospital care and prolonged hospital stay. Among the HAdV genotypes, HAdV B3 is common in Taiwan but HAdV B7 is strongly related to pneumonia. In this study, the risk of mortality is more related to the patient's underlying condition than to HAdV genotype.

Conflicts of interest

All authors declare that they have no conflicts of interest associated with the materials discussed in the article.

References

1. Lai CY, Lee CJ, Lu CY, Lee PI, Shao PL, Wu ET, et al. Adenovirus serotype 3 and 7 infection with acute respiratory failure in children in Taiwan, 2010—2011. *PLoS One* 2013;**8**:e53614.
2. Tsou TP, Tan BF, Chang HY, Chen WC, Huang YP, Lai CY, et al. Community outbreak of adenovirus, Taiwan, 2011. *Emerg Infect Dis* 2012;**18**:1825—32.
3. Sun Q, Jiang W, Chen Z, Huang L, Wang Y, Huang F, et al. Epidemiology and clinical features of respiratory adenoviral infections in children. *Eur J Pediatr* 2014;**173**:441—4.
4. Treacy A, Carr MJ, Dunford L, Palacios G, Cannon GA, O'Grady A, et al. First report of sudden death due to myocarditis caused by adenovirus serotype 3. *J Clin Microbiol* 2010;**48**:642—5.
5. Reyes-Andrade J, Sanchez-Cespedes J, Olbrich P, Falcon L, Sanchez-Ganfornina I, Tebruegge M, et al. Meningo-encephalitis due to adenovirus in a healthy infant mimicking severe bacterial sepsis. *Pediatr Infect Dis J* 2014;**33**:416—9.
6. Chau SK, Lee SL, Peiris MJ, Chan KH, Chan E, Wong W, et al. Adenovirus respiratory infection in hospitalized children in Hong Kong: serotype-clinical syndrome association and risk factors for lower respiratory tract infection. *Eur J Pediatr* 2014;**173**:291—301.
7. Pham TT, Burchette Jr JL, Hale LP. Fatal disseminated adenovirus infections in immuno-compromised patients. *Am J Clin Pathol* 2003;**120**:575—83.

8. Gray GC, McCarthy T, Lebeck MG, Schnurr DP, Russell KL, Kajon AE, et al. Genotype prevalence and risk factors for severe clinical adenovirus infection, United States 2004—2006. *Clin Infect Dis* 2007;**45**:1120—31.
9. Alharbi S, Van Caeseele P, Consunji-Araneta R, Zoubeidi T, Fanella S, Souid AK, et al. Epidemiology of severe pediatric adenovirus lower respiratory tract infections in Manitoba, Canada, 1991—2005. *BMC Infect Dis* 2012;**12**:55.
10. Madisch I, Harste G, Pommer H, Heim A. Phylogenetic analysis of the main neutralization and hemagglutination determinants of all human adenovirus prototypes as a basis for molecular classification and taxonomy. *J Virol* 2005;**79**:15265—76.
11. Wang SL, Chi CY, Kuo PH, Tsai HP, Wang SM, Liu CC, et al. High-incidence of human adenoviral co-infections in Taiwan. *PLoS One* 2013;**8**:e75208.
12. Hsieh WY, Chiu NC, Chi H, Huang FY, Hung CC. Respiratory adenoviral infections in Taiwanese children: a hospital-based study. *J Microbiol Immunol Infect* 2009;**42**:371—7.
13. Herbert FA, Wilkinson D, Burchak E, Morgante O. Adenovirus type 3 pneumonia causing lung damage in childhood. *Can Med Assoc J* 1977;**116**:274—6.
14. Yamamoto D, Okamoto M, Lupisan S, Suzuki A, Saito M, Tamaki R, et al. Impact of human adenovirus serotype 7 in hospitalized children with severe fatal pneumonia in the Philippines. *Jpn J Infect Dis* 2014;**67**:105—10.
15. Sung CC, Chi H, Chiu NC, Huang DT, Weng LC, Wang NY, et al. Viral etiology of acute lower respiratory tract infections in hospitalized young children in Northern Taiwan. *J Microbiol Immunol Infect* 2011;**44**:184—90.
16. Abd-Jamil J, Teoh BT, Hassan EH, Roslan N, AbuBaka S. Molecular identification of adenovirus causing respiratory tract infection in pediatric patients at the University of Malaya Medical Center. *BMC Pediatrics* 2010;**10**:46.
17. Xu W, McDonough MC, Erdman DD. Species-specific identification of human adenoviruses by a multiplex PCR assay. *J Clin Microbiol* 2000;**38**:4114—20.
18. Tamura K, Peterson D, Peterson N, Stecher G, Nei M, Kumar S. MEGA5: molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods. *Mol Biol Evol* 2011;**28**:2731—9.
19. Chang SY, Lee CN, Lin PH, Huang HH, Chang LY, Ko W, et al. A community-derived outbreak of adenovirus type 3 in children in Taiwan between 2004 and 2005. *J Med Virol* 2008;**80**:102—12.
20. Tang L, Wang L, Tan X, Xu W. Adenovirus serotype 7 associated with a severe lower respiratory tract disease outbreak in infants in Shaanxi Province, China. *Virol J* 2011;**8**:23.
21. Cheng CC, Huang LM, Kao CL, Lee PI, Chen JM, Lu CY, et al. Molecular and clinical characteristics of adenoviral infections in Taiwanese children in 2004—2005. *Eur J Pediatr* 2008;**167**:633—40.
22. Cooper RJ, Hallett R, Tullo AB, Klapper PE. The epidemiology of adenovirus infections in Greater Manchester, UK 1982—96. *Epidemiol Infect* 2000;**125**:333—45.
23. Hong JY, Lee HJ, Piedra PA, Choi EH, Park KH, Koh YY, et al. Lower respiratory tract infections due to adenovirus in hospitalized Korean children: epidemiology, clinical features, and prognosis. *Clin Infect Dis* 2001;**32**:1423—9.
24. Kwon YH, Lee HY. Differences of respiratory function according to level of the gross motor function classification system in children with cerebral palsy. *J Phys Ther Sci* 2014;**26**:389—91.