Adenovirus infection and subsequent risk of Kawasaki disease: A population-based cohort study

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Abstract

Background: The relationship between adenovirus infection and Kawasaki disease (KD) is unclear. The purpose of this study was to determine the relationship between adenovirus infection and KD using a cohort study in Taiwan.

Methods: We used Taiwan National Health Insurance data (from 2000 to 2008) to conduct a population-based cohort study, analyzing children that was under 18 years of age. In total, 5280 children had adenovirus infection, and 5280 children without adenovirus infection were matched and followed up. Subsequent KD was the major outcome event. The Cox proportional hazards model was used to estimate the hazard ratio (HR) with 95% confidence intervals (CIs) of developing KD associated with adenovirus infection.

Results: There was a significantly higher cumulative incidence of KD in the adenovirus-infected cohort than that in the control cohort (log-rank test, $p < 0.001$). In the adenovirus-infected cohort, overall incidence of KD was 5.29 times higher than that of the control cohort (adjusted HR 5.29, 95% CI: 2.48–11.3). Increased KD risk was associated with previous adenovirus infection in children aged 3–5 years, in female patients, in those with a low urbanization level, and in those with allergies.

Conclusion: An association between previous adenovirus infection and KD was identified in Taiwanese children, but other potential risk factors were not fully analyzed. The relationship between infection and KD requires further study.

Keywords: Adenovirus; Cohort study; Kawasaki disease

1. INTRODUCTION

Kawasaki disease (KD) occurs mainly in infants and children under 5 years of age, and its cause of KD is unknown.[1] Infection has long been considered a possible triggering factor for KD.[2] A strong association between KD and some viral infections has been reported.[2,3] These KD-related viruses included retrovirus, herpesviruses/parvoviruses, adenoviruses, coronaviruses, enterovirus, etc.[2,3]

KD and acute adenoviral infection share many clinical characteristics.[4] The major clinical criteria of KD is fever for at least 5 days plus four of five criteria (bilateral conjunctivitis; changes of the mucosa of the oropharynx-fissured lips/strawberry tongue; changes in the peripheral extremities such as edema and/or erythema of hands and/or feet, perianal desquamation; cervical lymphadenopathy more than 1.5 cm; and polymorphous skin rash).[1] In contrast, adenoviral infection present with many features suggestive of KD, including prolonged fever, skin rash, conjunctivitis, mucous membrane change, and adenopathy.[4] To avoid unnecessary intravenous immunoglobulin treatments, several diseases such as streptococcus infection, Epstein-Barr virus, measles, collagen vascular disorder, drug reaction, and adenovirus infection should be excluded.[2] Among these, the serious diagnostic challenge is posed by adenovirus infection.[4] Many children infected with adenovirus present with features resembling KD, especially incomplete KD.[4] This makes the association between KD and adenovirus infection become an important issue.

The Taiwan National Health Insurance (NHI) program covers most of the Taiwanese population (above 99%).[5] There are no previous reports on the association between KD and adenovirus infection that analyzed the reliable data collected by the NHI program. Hence, we proposed a study using the NHI databases to elucidate the association between adenovirus infection and KD in Taiwan.

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2. METHODS

2.1. Data source

We established the study on the basis of the child health database, a portion of NHI research database. The child health database comprises half of all insured children aged ≤18 years old between 1996 and 2008. The Taiwanese government followed them until the children reached 18 years of age. The child health database includes registry of beneficiary (including birthday, sex, parental occupation, residence, etc.), inpatient and outpatient files, and other medical service. The contracted medical facilities recorded the disease history for each insurant according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To safeguard people's privacy, the Taiwanese government deidentified patient data before releasing the database for research. This study was approved by the Ethics Review Board of China Medical University [CMUH104-REC2-115(CR-4)].

2.2. Study population

To research the association between adenovirus infection and KD risk, we organized a population-based cohort study. The adenovirus-infected cohort was established from children infected by adenovirus (ICD-9-CM: 079.0, 077.2, 077.3, 480.0, 079.1, and 008.62) between 2000 and 2008, and the index date was set as the first date of diagnosis of adenovirus infection for each patient. To avoid coding errors in the claims data, we included only children who had at least three clinic visits with the diagnosis of adenovirus infection. Adenovirus infection frequently presents with prolonged fever and typical clinical features, and patients may be brought to visit the clinic every 2–3 days during the same course of infection. We therefore defined patients with at least three consensus diagnoses to ensure diagnostic validity. Participants for the control cohort were selected from children without adenovirus infection. The control cohort was frequency matched by age, urbanization, and parental occupation at a 1:1 ratio. The index date for control subjects was assigned the same date of the matched cases. We excluded adenovirus-infected children and controls who developed KD before the index date. We followed the subjects from the index date until they were either removed from the health insurance program, turned 18 years old, developed KD, or followed up until December 31, 2012 if none of the aforementioned events occurred. The diagnosis of typical and atypical KD was based not only on ICD-9-CM code (ICD-9-CM code 446.1) but also on the Registry for Catastrophic Illness Patient Database, which includes selected serious injuries and illnesses. The database is published by the Department of Health, Executive Yuan, Taiwan. To be registered as having KD, the diagnosis must be confirmed and certificated by a board-certified specialist. The application is further reviewed and approved by the NHI Bureau, which ensures the validity of the diagnosis.

The confounders of the study were age, sex, parental occupation, urbanization, and comorbidity. An allergic disease (ICD-9-CM codes 493, 477, and 691.8) was deemed a comorbidity. According to the work place, parental occupation was classified into three groups: white-collar (working indoor), blue-collar (working outdoor), and other (retired, low, or no income). The white-collar group included public institutional workers, educators, and administrative personnel in business and industries. Blue-collar workers' occupations were characterized by longer hours of outdoor work and included fishing, farming, and industrial labor. The third group contained primarily retired, unemployed, and low-income populations. The criteria of the demarcating urbanization level included the population density (people/km^2), ratios of educational attainment, ratios of elderly people and agricultural workers, and the number of physicians per 100 000 people.[6] The highest and lowest levels of urbanization were assigned levels 1 and 4, respectively.

2.3. Statistical analysis

To characterize the adenovirus-infected cohort and control cohort, we presented mean age and the corresponding standard deviation, and the number and percentage of each category variables (such as sex, occupation, urbanization, and allergic disease). We used Student's *t* and chi-square tests to assess the distribution difference; the *t* test was used to compare age, and the chi-square test was used for the category variables. The incidence density of KD was calculated for the adenovirus-infected cohort and the control cohort. The cumulative incidence curves were measured using the Kaplan–Meier method. We applied the log-rank test to assess the curve difference. To evaluate KD risk in the two cohorts, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using single variable and multivariable Cox proportional hazard models. SAS 9.4 (SAS Institute, Cary, NC) was used to compute the analysis. R software (R Foundation for Statistical Computing, Vienna, Austria) was used to plot the incidence curve. The significant level was set at <0.05 for two-side testing of *p* values.

3. RESULTS

Table 1 presents the features of the adenovirus-infected and control cohorts. The study involved 5280 patients with previous adenovirus infection and the same number of controls. Because age, sex, urbanization, and parental occupation were matched, differences for these variables were not statistically significant between the groups. The mean ages of children in the adenovirus-infected and control cohorts were 4.48 ±3.28 and

Table 1

Comparisons in demographics and allergic disease between subjects with and without the adenovirus infection

	Adenovirus infection				
	No (n = 5280)		Yes (n = 5280)		
	n		n		*p*
Age, years, mean (SD)	4.48	(3.28)	4.47	(3.25)	0.95
Stratified age					0.99
≤2 (%)	1349	(25.6)	1349	(25.6)	
3–5 (%)	2050	(38.8)	2050	(38.8)	
>5 (%)	1881	(35.6)	1881	(35.6)	
Sex					0.99
Girl (%)	2441	(46.2)	2441	(46.2)	
Boy (%)	2839	(53.8)	2839	(53.8)	
Urbanization level[a]					0.99
1 (highest) (%)	1482	(28.1)	1482	(28.1)	
2 (%)	1572	(29.8)	1572	(29.8)	
3 (%)	1319	(25.0)	1319	(25.0)	
4 (lowest) (%)	907	(17.2)	907	(17.2)	
Parental occupation					0.99
White collar (%)	3558	(67.4)	3558	(67.4)	
Blue collar (%)	880	(16.7)	880	(16.7)	
Others[b] (%)	842	(16.0)	842	(16.0)	
Allergic disease					<0.001
No (%)	3646	(69.1)	3079	(58.3)	
Yes (%)	1634	(31.0)	2201	(41.7)	

Adenovirus-infected cohort: follow-up time 6.62 y (SD = 2.14).

Control cohort: follow-up time 6.69 y (SD = 2.15).

[a]The urbanization level was categorized by the population density of the residential area into four levels: level 1 as the most urbanized region and level 4 as the least urbanized region.

[b]Other occupations included primarily retired, unemployed, and low-income populations.

4.47 ± 3.25 years, respectively. The percentage of boys was 53.8%. Most children were members of families with higher socioeconomic status (urbanization 1 or 2: 57.9%; white collar: 67.4%). Prevalence of the allergic disease was higher in the adenovirus-infected cohort than in the control cohort ($p < 0.001$).

Table 2 indicates the risk of KD and risk stratified by age, sex, urbanization, parental occupation, as well as allergic disease between the groups. The incidence rate of KD was 11.7 and 2.26 per 10 000 person-years in the adenovirus-infected and control cohorts, respectively. As the Fig. 1 presents, the incidence curve for the adenovirus-infected cohort was significantly higher than that of the control cohort (p for log rank test < 0.001). After being adjusted for age, sex, urbanization, parental occupation, and allergic disease, the adenovirus-infected cohort had a 5.29-fold higher risk of KD than the control cohort (adjusted HR = 5.29, 95% CI = 2.48–11.3). Compared with the control cohort, adjusted HRs of KD risk were 3.57 (95% CI = 1.31–9.67) and 6.55 (95% CI = 1.96–21.9) in the adenovirus-infected cohort aged ≤2 and 3–5 years, respectively. Compared with the controls, girls with previous adenovirus infection had 9.16-fold higher risk of KD (adjusted HR = 9.16, 95% CI = 2.76–30.4), and boys with previous adenovirus infection had only a 3.08-fold higher risk (adjusted HR = 3.08, 95% CI = 1.13–8.39). Children with previous adenovirus infection had higher risk of KD than the controls regardless of urbanization level or parental occupation. Compared with the control cohort, the adjusted HRs of KD were 4.41 (95% CI = 1.801–10.8) and 6.99 (95% CI = 1.61–30.3) in the adenovirus-infected cohort without and with allergic disease, respectively.

Table 3 indicates the KD risk among various subtypes of adenovirus in the adenovirus-infected cohort. Children with the previous subtype of adenovirus infection, coded as ICD-9-CM 079.0, had a 5.49-fold higher KD risk than the controls (adjusted HR = 5.49, 95% CI = 2.57–11.7). The KD risk related to the other subtypes was not analyzed because no KD events occurred (adjusted HR = 6.04, 95% CI = 2.71–13.5).

Table 4 shows the KD risk stratified by the follow-up period for the adenovirus-infected and control cohorts. The results indicated that KD event occurred mostly in the follow-up period within 5 years. Children with previous adenovirus infection had a 6.04-fold higher KD risk than controls during this span.

4. DISCUSSION

Our study discovered significantly 5.29-fold higher KD risk in children with previous adenovirus infection, compared with controls. The risk of KD was particularly higher in children 3–5 years old, in females, in children with a low urbanization level,

Table 2

The risk of Kawasaki disease and shared hazard ratio for subjects with the adenovirus infection compared with those without the adenovirus infection by age, sex, urbanization level, parental occupation, and allergy in the Cox regression models

	Nonadenovirus infection			Adenovirus infection			Adjusted HR (95% CI)
	Event	Person-years	IR	Event	Person-years	IR	
Overall[a]	8	35 336	2.26	41	34 945	11.7	5.29 (2.48, 11.3)***
Stratified age[b]							
≤2	5	9546	5.24	16	9377	17.1	3.57 (1.31, 9.76)*
3–5	3	14 331	2.09	25	14 130	17.7	6.55 (1.96, 21.9)**
>5	0	11 460	0.00	0	11 438	0.00	…
p value for interaction							0.64
Sex[c]							
Girl	3	16 172	1.86	24	15 891	15.1	9.16 (2.76, 30.4)***
Boy	5	19 165	2.61	17	19 054	8.92	3.08 (1.13, 8.39)*
p value for interaction							0.28
Urbanization level[d,e]							
1 (highest)	4	10 046	3.98	16	9908	16.2	5.55 (1.83, 16.8)**
2	1	10 602	0.94	7	10 541	6.64	5.64 (0.69, 46.0)
3	1	8491	1.18	0	8497	0.00	…
4 (lowest)	2	6198	3.23	18	5999	30.0	7.71 (1.78, 33.4)**
p value for interaction							0.38
Parental occupation[f]							
White collar	7	24 064	2.91	41	23 696	17.3	6.07 (2.72, 13.5)***
Blue collar	0	6070	0.00	0	6027	0.00	…
Others[g]	1	5202	1.92	0	5223	0.00	…
p value for interaction							0.98
Allergic diseases[h]							
No	6	24 869	2.41	24	20 566	11.7	4.41 (1.80, 10.8)**
Yes	2	10 468	1.91	17	14 380	11.8	6.99 (1.61, 30.3)**
p for interaction							0.74

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

CI = confidence interval; HR = hazard ratio; IR = incidence rate per 10 000 person-years.

[a]Adjusted for age, sex, urbanization level, parental occupation, and allergy.

[b]Adjusted HR was calculated by Cox proportional hazard regression stratified by age and adjusted for sex, urbanization level, parental occupation, and allergy.

[c]Adjusted HR was calculated by Cox proportional hazard regression stratified by sex, and adjusted for age, urbanization level, parental occupation, and allergy.

[d]Adjusted HR was calculated by Cox proportional hazard regression stratified by urbanization level and adjusted for age, sex, parental occupation, and allergy.

[e]The urbanization level was categorized by the population density of the residential area into four levels: level 1 as the most urbanized region and level 4 as the least urbanized region.

[f]Adjusted HR was calculated by Cox proportional hazard regression stratified by parental occupation and adjusted for age, sex, urbanization level, and allergy.

[g]Other occupations included primarily retired, unemployed, and low-income populations.

[h]Adjusted HR was calculated by Cox proportional hazard regression stratified by allergy and adjusted for age, sex, urbanization level, and parental occupation.

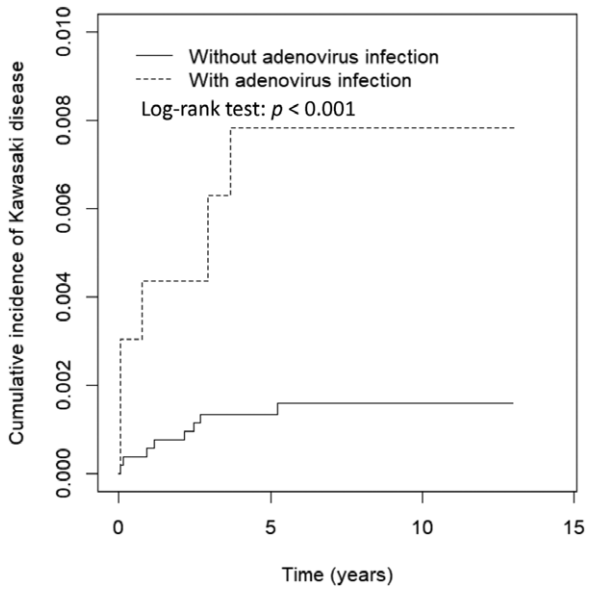

Fig. 1 Cumulative incidence of Kawasaki disease compared between subjects with and without adenovirus infection using the Kaplan–Meier method.

and in those with allergies. Children with previous adenovirus infection had a 6.04-fold higher KD risk than controls during a follow-up period of no more than 5 years. To our knowledge, this is the first population-based cohort study to reveal positive relationship between previous adenovirus infection and KD.

Reports about the association of KD and adenovirus are few and controversial. Okano et al.[4] detected percentage of adenoviral antibodies in KD patients. By contrast, Shike et al.[7] found no link between adenovirus and KD using adenovirus serology and quantitative polymerase chain reaction (PCR). Kim et al.,[8] also on the basis of PCR, reported no relation between adenoviral infection and KD occurrence (n = 14 267). However, the possible coexistence of KD and adenovirus cannot be denied. Embil et al.[9] detected adenovirus from a patient with fatal KD. Jordan-Villegas et al.[10] reported a KD case with adenoviral infection complicated with coronary artery aneurysm. Jaggi et al.[11] demonstrated that 8.8% (5/57) of typical KD and 25% (5/20) of atypical KD patients had adenovirus.[x] In Taiwan, Chang et al.[12] used PCR to reveal a higher rate of adenovirus infection in patients with KD (n = 226) than in normal controls (18% vs 4%, $p = 0.007$). Turnier et al.,[13] on the basis of PCR, reported 4.7% adenovirus (+) in patients with KD (n = 192). Fukuda et al.[14] reported the noteworthy case of the simultaneous development of KD following acute adenovirus infection in monozygotic twins. They speculated that KD was triggered by adenoviral infection and that specific immune responses to some pathogens, arising from genetic susceptibility, play a critical role in the occurrence of KD. Our cohort study, with its large sample and strong analytic power, demonstrated a close association between KD and previous adenovirus infection in Taiwan. The mechanism of adenoviral infection involved in KD requires further evaluation.

In this study, the relationship of KD and urbanization is difficult to determine. Our results indicated the significantly higher risk of KD in Taiwanese children with previous adenovirus living at a lower urbanization level. Harnden et al.[15] reported that urbanization is an independent risk factor for KD. Rapid economic development might have increased the occurrence of KD in Japan and Korea.[15] However, no association between urbanization and prevalence of KD in Taiwan was reported by Chang et al.[16] Additional investigation of the potential difference

Table 3

Incidence rate and hazard ratio of Kawasaki disease in the adenovirus-infected cohort by the subtype of adenovirus infection estimated using Cox regression models

Variable (ICD-9-CM)	No.	Event	Person-years	IR	Adjusted SHR[a] (95% CI)
Nonadenovirus infected cohort	5280	8	35 336	2.26	1 (Reference)
Subtype of adenovirus infection					
Adenovirus (079.0)	5102	41	33 588	12.2	5.49 (2.57, 11.7)***
Pharyngoconjunctival fever (077.2)	82	0	648	0.00	-
Acute adenoviral follicular conjunctivitis (077.3)	1	0	6	0.00	-
Pneumonia due to adenovirus (480.0)	1	0	5	0.00	-
Meningitis due to adenovirus (079.1)	0	0	0	0	-
Enteritis due to adenovirus (008.62)	94	0	697	0.00	-

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
CI = confidence interval; HR = hazard ratio; IR = incidence rate per 10 000 person-years; SHR = subhazard ratio.
[a]Adjusted for age, sex, urbanization level, parental occupation, and allergy.

Table 4

Comparison of incidence densities of Kawasaki disease hazard ratio by the follow-up period between subjects with and without the adenovirus infection

	Adenovirus infection							
	No			Yes				
	Event	Person-years	IR	Event	Person-years	IR	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Follow-up period (years)								
≤5	7	25 584	2.74	41	25 482	16.1	5.87 (2.63, 13.1)***	6.04 (2.71, 13.5)***
>5	1	9752	1.03	0	9464	0.00	…	…

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
CI = confidence interval; HR = hazard ratio; IR = incidence rate per 10 000 person-years.
[a]Adjusted for age, sex, urbanization level, parental occupation, and allergy.

between rural and urban populations is required to elucidate the effect of urbanization on KD occurrence.

High-income parental occupations were associated with the higher KD risk in this series. Compatible with our finding, Fujiwara et al.[17] demonstrated that higher household income was associated with increased KD incidence. The hygiene hypothesis was developed upon observing that a lack of exposure to infectious agents in early childhood might increase susceptibility to allergic diseases by suppressing the capacity of the immune system to modulate.[18,19] The hygiene hypothesis might partially explain the effect of high income on KD incidence. The relationship between KD and allergies has been well studied in Taiwan.[3,20–22] Our result is in agreement with these previous findings.[3,20–22] More prospective studies, including infectious factors, are required to elucidate the relationship between KD and allergies.

This study had several limitations. First, diagnoses of adenovirus infection using NHI data may be less accurate than those made according to culture reports and result in misclassification. This misclassification tends to underestimate the true relative risk of KD among children with adenovirus infection. Second, we used NHI databases from 2000 to 2008 without available procedure or drug codes to distinguish other viral infection. Third, other potential risk factors, including environmental factors, were not fully analyzed. However, because the NHI program covers almost the entire population, these data reflect the actual relationship between KD and previous adenovirus infection in Taiwan. Further studies elucidating the pathogenesis about the involvement of adenovirus infection in KD are warranted.

A higher association between previous adenovirus infection and KD was found in Taiwanese children, but not all potential risk factors were analyzed. The relationship between infection and KD requires further study.

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